

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
)
Reijo J. BACKSTROM *et al.*)
)
Patent No.: 5,446,194)
Issue Date: August 29, 1995) **ATTN: Box Patent Extension**
)
Application No.: 08/121,617)
Filed:)
)
For: PHARMACOLOGICALLY ACTIVE)
ACTIVE CATECHOL DERIVATIVES)

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DEC 17 1999

TRANSMITTAL AND APPLICATION
FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

This application is submitted by including an original, a certified copy and three working copies. Each copy contains five Exhibits:

- Exhibit 1 - FDA Approval Letter (4 pages)
- Exhibit 2 - Copy of Assignment (2 pages)
- Exhibit 3 - U.S. Patent No. 5,446,194 (22 pages)
- Exhibit 4 - Maintenance Fee Payment (1 page) and
- Exhibit 5 - Copy of the Power of Attorney (4 pages)

Pursuant to § 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, and in accordance with the provisions of 35 U.S.C. § 156 and 37 C.F.R. § 1.710 *et seq.*, the owner of record of U.S. Patent No. 5,446,194 ("the '194 Patent") requests that the term of the '194 Patent be extended 416 days to expire on October 19, 2013. The '194 Patent issued on August 29, 1995 on patent application Serial No. 08/121,617. The '194 Patent would, in view of GATT, and in the absence of an extended term, expire on August 29, 2012. The patent is assigned of record to Orion-yhtymä Oy, Orionintie 1, 02200 Espoo FINLAND (hereinafter referred to as "Applicant"). "Orion Corporation" or "Orion" is the parallel English business name to Orion-yhtymä Oy, and is also used in this application.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the numerical format set forth in 37 C.F.R. § 1.740 in §§ I-XVII.

BEST AVAILABLE COPY

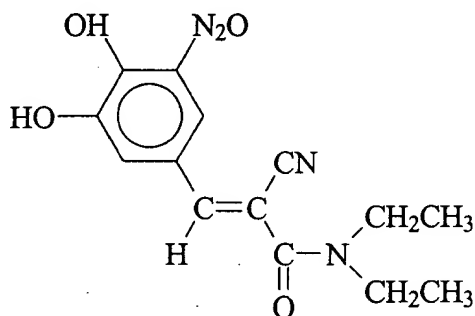
I. APPROVED PRODUCT

The approved product is COMTAN®. The active ingredient is entacapone.

Entacapone is designated chemically as (E)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide or (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

The empirical formula of entacapone is $C_{14}H_{15}N_3O_5$ and has a molecular weight of 305.29 daltons.

The structure of entacapone is as follows:



Mechanistically, COMTAN® is an inhibitor of catechol-O-methyl transferase (COMT), an enzyme involved in the metabolism of catecholamine neurotransmitters and related drugs.

COMTAN® is a pharmaceutical for treating patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing off" (so-called "fluctuating" patients). The approved product is marketed in the form of a 200 mg tablet to be used as an adjunct therapy to levodopa/carbidopa to treat patients with idiopathic Parkinson's Disease.

II. APPLICABLE FEDERAL STATUTE

The approved product, COMTAN®, was subject to regulatory review under Section 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA") 21 U.S.C. § 301 *et seq.*

Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

III. PRODUCT APPROVAL DATE

The approved product, COMTAN®, received permission for commercial marketing or use by the Food and Drug Administration ("FDA") pursuant to § 505(b) of the FFDCA on October 19, 1999. See Exhibit 1 (APPROVAL LETTER FOR COMTAN®).

IV. IDENTIFICATION OF DRUG PRODUCT INGREDIENTS

In accordance with 37 C.F.R. § 1.740(a)(4), the active ingredient of COMTAN® is entacapone. Entacapone has not been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act or the Virus-Serum-Toxin Act.

V. APPLICATION FILING DEADLINE

The present application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f). The last day on which the application can be submitted is December 20, 1999 (December 18, 1999 is a Saturday).

VI. PATENT FOR WHICH EXTENSION IS SOUGHT

The patent for which an extension is being sought is U.S. Patent No. 5,446,194 ("194 Patent"), which issued on August 29, 1995, in the names Reijo J. BACKSTROM, Kalevi E. HEINOLA, Erkki J. HONKANEN, Seppo K. KAAKKOLA, Pekka J. KAIRISALO, Inge-Britt Y. LINDEN, Pekka I. MANNISTO, Erkki A. O. NISSINEN, Pentti POHTO, Aino K. PIPPURI and Jarmo J. PYSTYNEN. The patent is assigned of record to Orion-yhtymä Oy, Orionintie 1, 02200 Espoo, FINLAND (for copy of Assignment, see Exhibit 2). The reel and frame number for the assigned patent is 4820/0619.

The application for the '194 Patent was filed September 16, 1993 and claims the benefit of priority under 35 U.S.C. § 120 dating back to November 27, 1987. Since this

patent was filed before June 8, 1995, the effective date of the Uruguay Round Agreements Act, it is entitled to a patent term of the longer of twenty (20) years from the earliest effective application U.S. filing date or seventeen (17) years from the patent issue date. For the '194 Patent, a patent term of seventeen (17) years from the issue date of August 29, 1995 is longer. The patent would thus expire, absent term extension, on August 29, 2012.

VII. COPY OF PATENT

A copy of the '194 Patent is enclosed herewith as Exhibit 3, including the entire specification and the claims.

VIII. COPY OF CERTIFICATE OF CORRECTION, DISCLAIMERS, MAINTENANCE FEE PAYMENT RECEIPTS OR REEXAMINATION CERTIFICATES

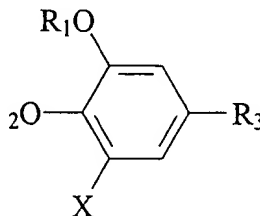
There are no certificate of correction, disclaimer or reexamination certificate for the '194 Patent. A copy of one maintenance fee payment receipt is enclosed in Exhibit 4.

IX. SHOWING THAT PATENT CLAIMS APPROVED PRODUCT

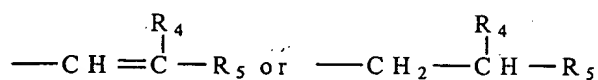
U.S. Patent No. 5,446,194 claims the approved COMTAN® product.

All four of the claims of the '194 Patent encompass the approved product as discussed in detail below:

1. A compound according to formula I



wherein R_1 and R_2 independently represent hydrogen, carbamoyl which is substituted by an alkyl of 1 to 4 carbon atoms, alkylcarbonyl of 2 to 5 carbon atoms or phenyl carbonyl, X represents nitro or cyano and R_3 represents



wherein R_4 represents cyano or alkylcarbonyl of 2 to 5 carbon atoms and R_5 represents carbamoyl which is unsubstituted or substituted with alkyl of 1 to 8 carbon atoms or which is substituted with hydroxyalkyl of 1 to 8 carbon atoms or pharmaceutically acceptable esters and salts thereof.

Entacapone has an R_4 group which is cyano and an R_5 group which is a carbamoyl substituted with an alkyl of 2 carbon atoms. Thus, Entacapone is encompassed by Claim 1.

2. The compound according to claim 1, wherein R_4 is cyano and R_5 is carbamoyl which is unsubstituted or substituted with alkyl of 1 to 3 carbon atoms.

Entacapone has an R_4 group which is cyano and a R_5 group which is a carbamoyl substituted with an alkyl of 2 carbon atoms. Thus, Entacapone is within the scope of Claim 2.

3. N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

Entacapone can be chemically designated as (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, which is a stereoisomer of the compound recited in Claim 3. Thus, the approved product is encompassed by Claim 3.

4. A compound selected from the group consisting of 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, N,N-dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide and N-isopropyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)-acrylamide.

Entacapone can be chemically designated as (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, which is a stereoisomer of a compound recited in Claim 4, *i.e.*, N,N-dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl) acrylamide. Thus, the approved product is within the scope of Claim 4.

X. INFORMATION PURSUANT TO 35 U.S.C. § 156(g)

The information required by 37 C.F.R. § 1.740(a)(10)(i) is set forth below.

An Investigational New Drug ("IND") application was filed by Orion-yhtymä Oy for entacapone on September 5, 1991. The IND became effective on November 29, 1991, eighty-five (85) days after the date of receipt of the IND. The IND number assigned to entacapone was IND 37,771.

A New Drug Application ("NDA") was filed by Orion-yhtymä Oy on January 2, 1998. The NDA number assigned to the application for COMTAN® was NDA 20-796. The NDA was approved on October 19, 1999.

Further, the above-identified patent is eligible for an extension of patent term since the following requirements of 35 U.S.C. § 156(g) are met:

- (1) the above-identified patent has not expired prior to the filing of this application for extension of patent term;
- (2) the term of the patent has never been extended;
- (3) the application for extension of patent term is being submitted by the agent for the owner of record of the '194 Patent for which a patent term extension is sought, who is a patent attorney authorized to practice before the U.S. Patent and Trademark Office (see attached Power of Attorney (Exhibit 5)), and who has general authority from said owner to act on behalf of said owner in patent matters including the execution of the APPLICATION FOR EXTENSION OF PATENT TERM being submitted pursuant to 37 C.F.R. § 1.740;
- (4) the product has been subject to a regulatory review period before its commercial marketing or use;
- (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

XI. ACTIVITIES DURING REGULATORY REVIEW PERIOD

Significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the dates applicable to such activities are as follows.

TABLE 1

Investigational New Drug (IND) Application (37,771) Entacapone Related Events

| Date | Submission contains: |
|--------------------|---|
| September 5, 1991 | Investigational new drug application |
| October 17, 1991 | Response to FDA request: -Changes to the report of Hazleton |
| October 28, 1991 | Response to FDA request for more information: - Final Study report 6753-544/23, Hazleton |
| December 2, 1991 | Oxford was notified by FDA that the clinical study could be initiated |
| December 10, 1991 | -Reference to the December 2, 1991 telephone conversation with the FDA a protocol amendment was provided - amendment 3 Dec. 91 / HH910010/0 |
| April 20, 1992 | - Protocol amendment HH920001/0 - Final protocol HH920006/1 - FDA FORM 1572/LeWitt - Rationale for 293928 |
| September 10, 1992 | Initial written report, safety report: - AER, patient 02 |
| September 22, 1992 | - Protocol amendment HH920009/1 |
| January 4, 1993 | Annual Progress Report - AKRO920034/1 |
| January 5, 1993 | Initially written report, safety report, S-008 - SAE, patient 15, USA |
| January 11, 1993 | Request for FDA meeting to review the results of the clinical studies summarized in - Status report KJ9200006/0 |

| Date | Submission contains: |
|-------------------|---|
| February 8, 1993 | Follow-up to a written report S-008: - completed form FDA 1639 |
| February 17, 1993 | Correspondence from the FDA, Ms. Katurah Higgins concerning Chemistry deficiencies in the IND |
| February 19, 1993 | List of people on behalf of Orion attending the March 3, 1993 meeting |
| March 2, 1993 | Initial written report, safety report: - AER, patient 3 |
| March 3, 1993 | FDA meeting |
| March 26, 1993 | Initial written report, safety report - AER, patient 7 - Amended protocol SR93003 |
| March 29, 1993 | - Minutes of the FDA meeting 3.3.93 - Final protocol AKRO920026/1 - Final protocol HH920011/1 |
| May 14, 1993 | - Overheads used on Meeting March 3, 93 - Curriculum/ Nutt, LeWitt, Kohler - 7A, 3.5.93 ILLA930001/1 - 7B, 3.5.93 - 7C, 3.5.93 - Final protocol TANA930016 |
| August 24, 1993 | - Curriculum/ Thulin, FORM 1572 - Curriculum/ Green, FORM 1572 - Amendment 1, HH93004/1 |
| August 25, 1993 | Initial written report: Study 2939035 - SAE, subject 004, Finland - SAE, subject 008, Finland - Final protocol AKRO930003/1 Study 2939039 - SAE, subject 10, Finland - Study protocol TANA930016/1 |

| Date | Submission contains: |
|-------------------|--|
| October 14, 1993 | - protocol AKRO930001/1, - curriculum/Eidelberg, - Inv. Br. June 1993 |
| December 13, 1993 | Information amendment (Chemistry) Response to the chemistry deficiencies outlined in Ms. Higgins' correspondence of 17 February 1993 - amendment to IND ILLA930017/0 |
| January 5, 1994 | Information amendment, results of two toxicology studies - 59/930295, Huntingdon - 58/930792, Huntingdon |
| January 6, 1994 | Annual Progress Report - AKRO930058/1 |
| January 27, 1994 | Request for End-of-Phase 2 meeting |
| February 22, 1994 | -Final protocol, HH930008/1, Study 2939044 - CV's (17 investigators) |
| February 25, 1994 | Information amendments: -Amendment to IND, Item 7, ILLA9940010 |
| March 18, 1994 | Information amendments (clinical) follow-up to a written report: - Updated investigator's brochure - Study report 2939042 (TANA930025/1) - CV / Nutt, LeWitt, Koller |
| March 25, 1994 | Initial written report - SAE, patient 008, Finland - protocol synopsis to study 293930 |
| March 31, 1994 | Response to FDA request for info - Discoloration of the urine by E. - Minutes of the FDA meeting 3.3.93 |
| April 4, 1994 | Initial written report - SAE, patient 012, |
| April 12, 1994 | Change in protocol - Amendment I to 2939044 (HH940003/1) |

| Date | Submission contains: |
|--------------------|--|
| May 3, 1994 | Request for end of phase 2 meeting with the division of neuropharmacological drugs. - Summary of data on the development of Entacapone, KJ940001/0 |
| June 22, 1994 | Other: Adverse experiences - SAE: patient 21, 293930, ENT9411, Finland - SAE, patient 286, Seesaw-study, USA |
| June 23, 1994 | Conference call minutes, June 2, 94: - discoloration of the urine by Entacapone - blindness evaluation form - research subject consent form |
| July 12, 1994 | - Form 1572 and CV of Dr. Lang - Second amendment to study protocol No 2939044, HH94005/1 - third amendment to study protocol No 2939044, HH94006/1 |
| July 13, 1994 | Transfer of clinical study monitoring - Orion-Farmos, Kansas established |
| July 14, 1994 | Follow-up to a written report: - SAE, patient 286, USA - form 1572 for Dr. A. Feigin |
| August 5, 1994 | Information on foreign clinical study: - protocol 2939033, MIVA930001/1 - list of centers and investigators, April 25, 94 - status May 9, 94 - FDA 1572's and CV's |
| August 12, 1994 | A Letter from Dr. Leber, comments on the Biopharmaceutics section |
| September 12, 1994 | Initial written report -SAE, patient 4109, Sweden, 2939034, ENT9420 |
| September 29, 1994 | Response to FDA request for information. Referring to FDA review of the biopharmaceutics section of supplement submission on Entacapone (S-030) |
| September 28, 1994 | Initial written report, follow-up to a written report - SAE, patient 4103, Sweden, 2939034, ENT9420 - AER, 2939044, SEESAW, patient 184, USA |
| October 13, 1994 | Follow-up to a written report: - SAE, patient 184, SEESAW, USA, ENT9422 |

| Date | Submission contains: |
|-------------------|---|
| October 14, 1994 | Change in protocol: - study protocol 2939054 |
| November 28, 1994 | Additional information: - 1572 Forms |
| November 29, 1994 | Information amendments: - Toxicological summary explaining the study results (HERA940005) - Investigator's letter / findings of the rat carcinogenicity study - study protocol IRI 450970: 104 week carcinogenicity study in rats by gavage |
| December 7, 1994 | Initial written report: - AER, 2939044, patient 370, ENT9437, Canada - SAE, 2939044, patient 364, Canada - AER, 2939034, patient 4605, ENT9434, Sweden Follow-up to a written report: - AER, 2939034, patient 4202, ENT9423, Sweden - SAE, 293930, patient 004, ENT941, Finland - SAE, 2939044, patient 366, ENT9432, Canada - AER, 293930, patient 008, ENT943, Finland (sent to FDA as S-026) - AER, 293930, patient 012, ENT944, Finland (sent to FDA as S-028) - AER, 293930, patient 021, ENT9411, Finland (sent to FDA as S-031) |
| December 13, 1994 | Response to FDA request for information: - C.V.'S for subinvestigators Lauren Abrey, Carolyn Cook, Karin Graefe |
| December 28, 1994 | General correspondence: - phase III protocol: request for FDA's opinion of the number of patients and duration of treatment |
| January 5, 1995 | Initial written report: - SAE, subject 262, 2939054, USA |
| January 13, 1995 | New protocol: - 2939061, HH940010/1 21.12.94 |
| January 13, 1995 | Initial written report: - SAE, 2939044, patient 270, USA - AER, 2939033, patient 4105, Sweden (ENT9414) - AER, 293930, patient 20, Finland (ENT9412) |
| January 13, 1995 | Annual report: - NINI940001/0 |

| Date | Submission contains: |
|-------------------|---|
| January 17, 1995 | Clinical plan: - Outline of continuation of clinical plans |
| January 23, 1995 | Revised 1572s of investigators: - Juncos, Greene, Kurlan, Jankovic, Shannon |
| February 3, 1995 | Letter from FDA, statistical comments on protocol 2939044 |
| February 21, 1995 | Other information: request for meeting, biopharmaceutics information - Pre-meeting information MKAH940007 - outlines of protocols 2939057, 2939058, 2939054 - tablet and raw material batches used in clin. studies |
| February 27, 1995 | Change in protocol: - 2939061, amend I, HH950002/1 |
| February 27, 1995 | Change in protocol: - 2939054, amend I, HH950001/1 |
| February 28, 1995 | Initial written report, safety report: - AER, patient 106, 2939054, USA |
| March 7, 1995 | Initial written report, safety report: - AER, subject 4201, 2939034, Sweden |
| March 7, 1995 | Follow-up to a written report: - letter: A Gordin, 27.2.95 to clarify the circulatory collapse adverse events of patients listed in the annual report (S-021) - patient 2/293913 - patient 18/293926 - patient 4/2939033 - patient 8/293915A |
| March 16, 1995 | Other: 1572 forms and Curricula Vitae for 17 investigators |
| March 20, 1995 | Initial written report, follow-up to a written report: - AER, patient 4303, 2939034, Sweden |
| March 23, 1995 | Initial written report, follow-up to a written report: Safety report - AER, patient 3403, 2939034, ENT9510, Norway |
| March 30, 1995 | Follow-up to a written report: - AER, patient 364, Seesaw, Canada |
| March 31, 1995 | Other: Agenda/list of attendees for teleconference to be held April 18, 95 |

| Date | Submission contains: |
|----------------|---|
| April 4, 1995 | Initial written report, safety report: - AER, patient 041, 2939054, ENT9517, USA |
| April 7, 1995 | Other: Investigator's Brochure March -95, MKAH950008/1 |
| April 11, 1995 | Other: Study report 2939060, TANA950003/1 |
| April 17, 1995 | Follow up to a written report, safety report: - AER patient 3404 (2939034, ENT9510, Norway) - SAE patient 330 (2939044, USA) - AER patient 061 (2939054, ENT9520, USA) |
| April 18, 1995 | Telephone conversation R. McCormack - R. Baweja, re-scheduling of the teleconference |
| April 19, 1995 | Other: Confirmation for the Biopharmaceutics Teleconference |
| April 21, 1995 | Biopharmaceutics Teleconference |
| April 25, 1995 | Initial written report, safety report: - AER, patient 107 (ENT9522, USA) |
| April 25, 1995 | Other: Confirmation of FDA Meeting to discuss Biopharmaceutics Issues, May 12, 1995 |
| May 3, 1995 | Other: Request for a meeting with the Neuropharmacology Division at FDA - FDA O-F correspondence 1994, HH950003/0 |
| May 3, 1995 | Other: revised 1572 forms (J. Juncos, C. Shults) |
| May 5, 1995 | IND safety report, initial written report: - AER, patient 029 (ENT9524, USA) |
| May 12, 1995 | FDA Meeting to discuss Biopharmaceutics Issues |
| May 25, 1995 | Initial written report, safety report: - AER, patient 2118 (2939033, Finland) - AER, patient 330 (ENT9530, 2939054, USA) |
| June 2, 1995 | Initial written report, safety report: - AER, patient 012, 2939054, ENT9528, USA |

| Date | Submission contains: |
|---------------|--|
| June 5, 1995 | Other: meeting package information - Meeting with the Neuropharmacology Division at FDA: - List of O-F and Oxford Res Attendees - Background for items to discuss, MKAH950009/1 - Detailed supportive information, MKAH950010/1 |
| June 8, 1995 | Other, revised FDA form 1572s: - CV / James Bennett Information amendments, pharmacology / toxicology: - LSR report 94/ORP040/0561 - LSR report 94/ORP041/0686 - LSR report 94/ORP02/0583 - LSR report 94/ORP03/0813 |
| June 15, 1995 | Initial written report: - AER, patient 302, 2939061 (ENT532, USA) |
| June 19, 1995 | F. Abramsek requests for copies of submission S-076 |
| June 19, 1995 | Response to FDA request for information: copies of submission S-076 |
| June 20, 1995 | IND safety reports, initial written report: - AER, patient 012 (ENT9528, USA) - AER, patient 307 (ENT9535, USA) |
| June 27, 1995 | Other: response to statistical issues, HERI950001 |
| July 10, 1995 | Other: draft FDA meeting minutes, May 12, 1995 HH950005/1 |
| July 18, 1995 | Information amendments: pharmacology/toxicology: - HRC report 68/943243 |
| July 18, 1995 | Response to FDA request (meeting on May 12, 1995) for information, study reports: - 2939035, SIRA940001/1 - 293925, AKRO940007/1 - 2939047, AKRO940015/1 - 293905, AKRO910016/0 - 293920, AKRO930011/1 - 2939050, TANA940006/1 - Dissolution data, 9.6.95 |

| Date | Submission contains: |
|--------------------|---|
| July 21, 1995 | Information amendments: pharmacology/toxicology (requested on meeting May 12, 1995): - CR92032030058, MAK920005 - Wikberg et al, -94 - Wikberg et al, -93 - Wikberg et al, -93 - CR90032870017, TW900003 - CR89032870004, AKRO890005 - CR89032870005, TW900001 - CR91032870033, TW910003 - Metabolism, MKAH950012 - CR95031210228, TW950001 - Protein binding, MKAH950011§ |
| July 25, 1995 | IND safety reports, initial written report: - AER, patient 189, 2939054 (ENT9543, USA) |
| August 2, 1995 | Initial written report, safety report: - SAE, patient 4202 (2939034, ENT9546, Sweden) |
| August 11, 1995 | FDA Meeting |
| August 17, 1995 | Initial written report, safety reports: - SAE, patient 0158 (2939052, ENT9544, Finland) - SAE, patient 409 (2939061, ENT9549, USA) |
| August 23, 1995 | Initial written report, safety reports: - SAE, patient 0552 (2939052, ENT9555, Finland) - SAE, patient 404 (2939061, ENT9550, USA) |
| September 6, 1995 | Initial written report, safety reports: - SAE, patient 326 (2939054, ENT9556, USA) - SAE, patient 302 (2939061, ENT9532, USA) |
| September 12, 1995 | Follow up to a written report, safety report: - SAE, patient 411 (2939061, ENT9566, USA) - SAE, patient 370 (2949044, Canada) |
| September 15, 1995 | Other: Meeting Minutes Aug. 11, 1995 + overheads used during the meeting |
| September 19, 1995 | Initial written report, safety report - SAE, patient 281 (2939054, ENT9574), USA - SAE, patient 42 (2939054, ENT9575), USA |

| Date | Submission contains: |
|-------------------|---|
| October 3, 1995 | Other: FDA request on Meeting Aug 11, 1995. Statistical analysis plans. - TUKY950001 (2939033) - HERI950002 (2939044) |
| October 10, 1995 | Initial written report, safety report: - AER, patient 3316 (2939034, ENT9580, Norway) - AER, patient 0158 (2939052, ENT9581, Finland) |
| October 12, 1995 | Safety report: - AER, patient 370 (2939044, Canada) |
| October 18, 1995 | Initial written report, follow up to a written report, safety report: - AER, patient 0501 (2939052, Finland) - AER, patient 0109 (2939052, Finland) - AER, patient 262 (2939054, USA) |
| October 31, 1995 | Initial written report, safety report: - AER, patient 326 (2939054, USA) |
| November 8, 1995 | Initial written report, safety report: - AER, patient 0158 (2939052, Finland) |
| November 27, 1995 | Follow-up to a written report, safety report: - AER, 2939034, patient 3316, Norway (ENT9580) - AER, 2939052, patient 0158, Finland (ENT9581) - AER, 2939054, patient 307, USA (ENT9535) |
| November 28, 1995 | Revised 1572s for - 2939054: J. Jankovic, G. Paulson, R. Pahwa, M. Mark - 2939061: R. Pahwa CV - 2939054, 2939061: J. Hubble |
| December 28, 1995 | Initial written report: - AER, 2939054, patient 281, USA (ENT9574) Initial and follow-up to a written report: - AER, 2939034, patient 4702, Sweden (ENT9596) |
| January 19, 1996 | Initial written report: - SAE, 2939054, patient 041, USA (ENT963) - SAE, 2939052, patient 0301, FIN (ENT964) Correction page regarding S-102 (Dec 28, 95), AER, 2939054, patient 281, USA (ENT9574) - page III treatments |

| Date | Submission contains: |
|------------------|--|
| February 1, 1996 | Follow-up to a written report: - SAE, patient 42, 2939054, USA (ENT9575) |
| February 2, 1996 | Annual report MKAH950014/1 |
| March 5, 1996 | Initial written report: - SAE, patient 0301, 2939052, Fin (ENT964) Follow-up to a written report (S-103) - SAE, patient 1610, 2939052, Fin (ENT9621) other: revised 1572: - Dr. Margery Mark, 2939044 |
| March 19, 1996 | Follow-up to a written report (S-102): - SAE, patient 4702, 2939034, SWE, ENT9596 |
| March 29, 1996 | Follow-up to a written report (S-070): - SAE, patient 107, 2939054 USA, ENT9522 |
| April 3, 1996 | Initial written report: - SAE, patient 4105, SWE, 2939033, ENT9414 Follow-up to a written report (S-108): - Corrected page, patient 107, 2939054, ENT9522 (Sponsor's summary) |
| April 26, 1996 | Initial written report: - SAE, patient 283, 2939054 USA, ENT9647 |
| April 30, 1996 | Other: - revised Investigator's Brochure MKAH960001/1, January 1996 |
| May 1, 1996 | Initial written report: - SAE, patient 411, 2939061 USA, ENT9649 |
| May 6, 1996 | Follow-up (S-075, S-080): - SAE, Patient 012, 2939054, USA, ENT9528 Follow-up (S-103, S-106): - SAE, patient 0301, 2939052, FIN, ENT964 |

| Date | Submission contains: |
|--------------------|--|
| July 2, 1996 | Information amendments: Pharmacology/Toxicology - Internal study report F93061210438, LESO950003, Finland 1996, vol 1 - IRI report 11353, Scotland 1996, vol 2-3 - IRI report 11312, Scotland 1996, vol 4-5 - F95101210622, KRHA960007, Finland 1996, vol 6 - J.P. Finn: Histological study report, Finn International, England 1995, vol. 6 - Huntingdon Life Sciences report 95/ORP048/0300, England 1995, vol. 6 - Internal study report F95101210605, Finland 1996, vol. 6 - Huntingdon Life Sciences report 95/ORP050/0500, England 1995 |
| July 12, 1996 | Initial written report: - Expedited AER, patient 0755, Finland, 2939052, ENT9688 initial |
| July 19, 1996 | Initial written report: - Expedited AER, patient 4204, Sweden, 2939034, ENT96102 initial |
| August 8, 1996 | Initial written report: - Expedited AER, patient 0402, 2939063, Germany, ENT96111 initial Follow-up to a written report (S-116): - patient 0755, Finland, ENT9688, 2939052, sponsor summary Other: revised 1572 for Dr. Kurth, 2939054 |
| August 29, 1996 | Other: revised 1572 for Dr J. Jankovic + CV for Dr. C. Sankhla (sub-investigator) |
| September 6, 1996 | Initial written report: - Expedited AER, patient 1501, 2939063 Germany, ENT96131 |
| September 25, 1996 | Follow-up to a written report (S-120) - Expedited AER, patient 1501, 2939063 Germany, ENT96131 |
| October 2, 1996 | Follow-up to a written report (S-116) - 2939052: Expedited AER, patient 0755, Finland, ENT9688 initial - 2939054: Revised 1572 for Dr. Kurlan |
| October 31, 1996 | Information amendment: - Chemistry, manufacturing and controls, ILLA960009/1 |
| December 16, 1996 | Initial written report: - Expedited AER, patient 0413, USA, ENT96182 (death) |

| Date | Submission contains: |
|-------------------|---|
| December 17, 1996 | Initial written report: - Expedited AER, patient 1651, Germany, ENT96179 |
| January 3, 1997 | Follow-up to a written report - 2939054: Expedited AER, patient 029, ENT9524, USA, (S-073) - 2939054: Expedited AER patient 283, USA, ENT9647 (S-110) - 2939052: Expedited AER, patient 0109 2939052, Finland, (S-097) |
| January 3, 1997 | Information amendments: chemistry and microbiology: - Huuhtanen, Dec. 17, 1996 (changing the status of Enta-III-X from an intermediate compound to a starting material). |
| January 3, 1997 | Initial written report: - 2939062: Expedited AER, patient 1911, Finland, ENT971 - 2939065: Expedited AER, patient 0657, UK, ENT96185 - 2939073: Expedited AER, patient 1558, Germany, ENT96186 |
| January 13, 1997 | Revised 1572's: - 2939054: Dr. J. Tertrud, Dr. A. Lang, Dr. J. Hammerstad - 2939061: Dr. J. Hammerstad |
| January 22, 1997 | Initial written report: - 2939062: Expedited AER, patient 0456, Finland, ENT9711 (death) |
| January 23, 1997 | Information amendments: chemistry and pharmacology: Item 7a, M. Tuominen Dec. 30, 1996 |
| January 31, 1997 | Initial written report: - 2939034: Expedited AER, patient 4402, Sweden, ENT9722 (death) |
| February 10, 1997 | Initial written report - 2939073: Expedited AER, patient 1571, ENT9729, Germany |
| March 6, 1997 | Annual report 1996, HEJ1970001/1 |
| March 6, 1997 | Follow-up to a written report - 2939034: Expedited AER, patient 4402, ENT9722, Sweden (S-133) - 2939061: Expedited AER, patient 411, ENT9566, USA (S-091) |
| March 21, 1997 | New correspondence: a summary of the telephone conversations between Dr. Rzeszotarski/FDA and P. Kosmoski/Oxford (January 13, 15 and 23, 1997) |

| Date | Submission contains: |
|-------------------|--|
| April 3, 1997 | Follow-up to a written report - 2939073: Expedited AER, patient 1571, Germany, ENT9729 (S-134) Revised 1572's - 2939054: Dr. M. Kurth, Dr. J. Juncos |
| May 13, 1997 | Initial written report: - 2939065: Expedited AER, patient 1103, GBR, ENT9771 - 2939054: Expedited AER, patient 261, USA, ENT9773 |
| May 29, 1997 | Other: Documentation of the telephone conversation on May 27, 1997, between Dr. Robert McCormack and Ms. Teresa A. Wheelous where the results of FDA's review of S-143 were transmitted |
| May 30, 1997 | Initial written report: - 2939054: Expedited AER, patient 314, USA, ENT9793 Follow-up to a written report: - 2939062: Expedited AER, patient 1911, FIN, ENT971 |
| June 17, 1997 | Initial written report: - Expedited AER, patient 167, USA, ENT970107 |
| July 25, 1997 | Follow-up to written report: - 2939061: Expedited AER, patient 409, ENT9549 (initial S-088) - 2939073: Expedited AER, patient 1558, ENT96186 (initial S-127) |
| December 10, 1997 | Initial written report: - 2939073: expedited AER, patient 2551, DEU, ENT97192, CTX 06043/0019/A |
| March 12, 1998 | Annual report 1997, PAWA980001/1 |
| March 19, 1998 | Initial written report: - Expedited AER, patient 1151, USA, ENT9839, CTX 06043/0019/A |
| May 4, 1998 | Change in protocol: - Second amendment to study protocol 2939054, 21.10.97 - Second amendment to study protocol 2939061, 21.10.97 Revised 1572s, 2929054: S. Factor, P. Greene, J. Growdon, M. Kurth, J. Juncos, A. Lang, M. Mark, G. Paulson, R. Pahwa, K. Shannon, R. Kurlan, J. Jankovic, C. Waters, J. Hammerstad, R. Kurlan Revised 1572s, 2929061: R. Pahwa, J. Hammerstad |

| Date | Submission contains: |
|-------------------|--|
| June 11, 1998 | Information amendments: chemistry /microbiology: CMC (SAMA980002) |
| July 7, 1998 | Initial written report: - 2939034: expedited AER, patient 2112, ENT9882 |
| July 15, 1998 | Initial written report: - 2939069: expedited AER, patient 0101, ENT9889 Revised 1572s, 2939054: Roger Kurlan, Margery Mark (corrected copy of S-158 received on September 3, 1998, previous version had Dr. Kurlan's 1572 form omitted) |
| August 6, 1998 | Safety report: Initial written report - 2939069: expedited AER, patient 0559, GBR, ENT9890 - 2939073: expedited AER, patient 0152, AUT, ENT9892 |
| August 26, 1998 | Safety report: Initial written report - 2939073: expedited AER, patient 2102, DEU, ENT98103 |
| August 28, 1998 | Safety reports: Follow-up to a written report - 2939073: expedited AER, patient 0152, AUT, ENT9892 - 2939069: expedited AER, patient 0101, GBR, ENT9889 (death) - 2939065: expedited AER, patient 1103, GBR, ENT9771 - 2939054: expedited AER, patient 247, USA, ENT9831 (death) |
| September 3, 1998 | - letter regarding S-158, S160, S-161 |
| October 19, 1998 | Safety report, Initial written report - 2939054: expedited AER, patient 045, USA, ENT98127 - letter dated October 28, 1998 |
| March 1, 1999 | Change in designation of US Agent - letter dated: February 24, 1999 |
| March 1, 1999 | Initial safety report - sudden death - expedited AER, patient MZ, DEU, ENT9914 - letter dated: February 26, 1999 |
| April 12, 1999 | Initial safety reports - ENT9951, GBR, patient died - ENT9916, SWE - ENT9953, DEU |

| Date | Submission contains: |
|-----------------|---|
| April 16, 1999 | Initial safety reports - ENT9963, GBR, patient died - ENT9956, GBR |
| April 23, 1999 | Initial safety reports - ENT9965, GBR - ENT9983, GBR |
| April 26, 1999 | Follow-up safety report - ENT9983, GBR |
| April 27, 1999 | Initial safety reports - ENT99100, GBR - ENT99101, GBR |
| May 15, 1999 | Initial safety reports - ENT99123, DNK - ENT99124, DNK |
| June 11, 1999 | Initial and follow-up safety report - ENT992, GBR |
| June 18, 1999 | Annual report -98, 100 and 200 mg tablets. Period: 16 Nov 1997 - 15 Nov 1998, AIHO990001/1, 8.6.99 |
| July 1, 1999 | Initial safety report - ENT99168, GBR - ENT99177, IRL |
| July 8, 1999 | Initial and follow-up safety report - ENT99173, GBR |
| July 13, 1999 | Letter of cross-reference |
| July 23, 1999 | Follow-up safety report - ENT99177, IRL |
| August 6, 1999 | Initial safety report - ENT99221, SWE - ENT99214, DEU |
| August 19, 1999 | Initial safety report - ENT99227, GBR |

Patent No. 5,446,194
Application No. 08/121,617
Attorney's Docket No. 020325-053

| Date | Submission contains: |
|--------------------|--|
| August 27, 1999 | Initial safety report - ENT99230, DEU |
| September 3, 1999 | Initial safety report |
| September 13, 1999 | Initial and follow-up safety report - ENT99231, GBR |
| September 15, 1999 | Initial safety report - ENT99298, DEU |
| September 17, 1999 | Response to requests of 13.9.99 regarding adverse event report - ENT99227 (S-178) |
| October 13, 1999 | Initial safety report |

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Attorney's Docket No. 020325-053

TABLE 2
New Drug Application (20-796)
COMTAN® Tablet, 200 mg (Entacapone) Related Events

| Date | Responsible | Subject |
|-------------------|------------------------------|--|
| December 4, 1996 | Orion / Oxford Research Int. | Request for pre-NDA-meeting |
| February 19, 1997 | Orion / Oxford | Pre-NDA-Meeting Package |
| March 6, 1997 | Orion / Oxford | Pre-NDA-Meeting List of Attendees |
| March 13, 1997 | Orion / Oxford | Correction to the Pre-NDA-Meeting Package |
| March 20, 1997 | | Pre-NDA-Meeting |
| April 4, 1997 | Orion / Oxford | To confirm the meeting of CMC-issues between Orion and Oxford personnel and the FDA chemists |
| April 7, 1997 | Orion / Oxford | Response to FDA request for information during the Pre-NDA-Meeting |
| April 14, 1997 | | Meeting with FDA to discuss the CMC-issues |
| April 30, 1997 | Orion / Oxford | Meeting Minutes, March 20, 1997 and April 14, 1997 were sent to FDA |
| May 29, 1997 | Orion / Oxford | Documentation of the telephone conversation on May 27, 1997, between Dr. R. McCormack and Ms. T. Wheelous where the results of FDA's review of information provided April 7 were transmitted |
| October 24, 1997 | Orion | Appointment of new agent Target Research Associates to act as the US agent for the New Drug Application (#20,796) Comtan® Tablet, 200 mg (Entacapone) Appointment Letter was included in the NDA submission |
| October 24, 1997 | Orion / Target | Initial Filing of New Drug Application (20-796) Comtan® Tablet, 200 mg (Entacapone) |
| October 28, 1997 | FDA / T. Wheelous | Request from FDA for a diskette of package insert. |

| Date | Responsible | Subject |
|---------------------|--------------------|--|
| October 30, 1997 | FDA | Date of Application 24 October 1997 Date of Receipt of Application 24 October 1997 |
| October 30, 1997 | Orion / Target | Three additional desk copies were sent to the FDA as requested by phone |
| November 4, 1997 | Orion / Target | A diskette of Annotated Package Insert was sent to Theresa Wheelous |
| December 1, 1997 | FDA / J. Knudsen | Medical questions regarding review of Entacapone NDA for fileability |
| December 3, 1997 | FDA / T. Wheelous | T. Wheelous required additional information to determine the fileability of the Entacapone NDA. 1. Submission of patient narratives 2. Electronic submission of the carcinogenicity study data |
| December 4, 1997 | FDA / T. Wheelous | T. Wheelous informed that the Entacapone NDA was not fileable |
| December 5, 1997 | Orion / Target | Electronic submission of the carcinogenicity study data |
| December 11, 1997 | FDA / J. Choudhury | Results of statistical reviewer of Entacapone |
| December 14, 1997 | Orion / Target | Submission of narrative summaries |
| December 15, 1997 | FDA / Rusty Katz | Dr. Rusty Katz contacted to discuss the reasons for refusal |
| December 19, 1997 | Orion / Target | The sponsor requested FDA to issue a refusal to file letter |
| December 23, 1997 | FDA / P. Leber | Letter to refuse the file |
| December 23, 1997 | Orion / Target | Entacapone NDA resubmitted to the FDA |
| December 30, 1997 | Orion / Target | Submission of additional statistical information requested by Dr. Japobrata Choudhury on December 11, 1997 |
| January 2 (8), 1998 | FDA | User fee payment was received. Application has been accepted as of January 2, 1998 |
| February 19, 1998 | FDA/ T. Wheelous | NDA was accepted for filing |

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Application No. 08/121,617
Attorney's Docket No. 020325-053

| Date | Responsible | Subject |
|-------------------|-------------------|--|
| February 23, 1998 | FDA / T. Wheelous | Request for additional copies of information |
| February 27, 1998 | Orion / Target | Submission of investigator list for adequate and well-controlled trials contained in NDA 20-796 |
| February 27, 1998 | Orion / Target | Additional copies requested on 23 February were sent |
| April 7, 1998 | FDA / T. Wheelous | Request to investigate the Environmental Assessment (EA) for Entacapone NDA |
| April 20, 1998 | FDA / T. Wheelous | Request for additional copies |
| April 22, 1998 | Orion / Target | Additional copies were sent |
| April 24, 1998 | Orion / Target | Environmental Assessment (EA) for Entacapone NDA was replaced with documentation supporting categorical exclusion) |
| April 30, 1998 | FDA / T. Wheelous | FDA could not locate the diskettes for the case report form tabulations |
| May 1, 1998 | Orion / Target | Amendment to add an alternative packaging site for dosage form |
| May 4, 1998 | Orion / Target | Diskettes requested on 30 April 98 were sent |
| May 6, 1998 | FDA / T. Wheelous | Request for Additional Information |
| May 8, 1998 | Orion / Target | Stability Update Amendment on the Dosage Form |
| May 15, 1998 | Orion / Target | Submission of the 120 Day Safety Update Report |
| June 17, 1998 | FDA / T. Wheelous | Request for an additional desk copy of Volume 3 of the 120 day safety update |
| June 18, 1998 | Orion / Target | Copy requested on 17 June was sent |
| July 29, 1998 | FDA / M. Sevka | Request for additional copies of Orion Studies 2939033, 2939044 and 2939052 |
| July 30, 1998 | FDA / T. Wheelous | Request for additional copies of study report/SAS data sets Nomenclature committee decision |

| Date | Responsible | Subject |
|--------------------|-----------------------|--|
| July 31, 1998 | FDA / M. Sevka | Clarification on the coding used for the CRF tabulations |
| August 3, 1998 | Orion / Target | Copies requested on 29 July were sent |
| August 3, 1998 | FDA / M. Sevka | Clarification on the glossary of adverse events |
| August 5, 1998 | Orion / Target | Information requested on 30 and 31 July was sent to FDA |
| August 7, 1998 | FDA / T. Wheelous | Request for SAS Data Sets |
| August 10, 1998 | FDA | FDA's preliminary review (dated August 4) of the CMC section |
| August 11, 1998 | Orion / Target | Information requested on 3 August was sent |
| August 12, 1998 | FDA / J. Choudhury | Request for additional information for the Entacapone |
| August 14, 1998 | Orion / Target | SAS data sets requested on 7 August were sent |
| August 18, 1998 | FDA / J. Choudhury | Follow-up to statistical information |
| August 18, 1998 | FDA / M. Sevka | Questions concerning review of the safety data for the Entacapone NDA |
| August 19, 1998 | FDA / R. Tresley | Request for a list of countries where Entacapone is approved for marketing |
| August 21, 1998 | FDA / R. Tresley | Request for additional information |
| August 27, 1998 | Orion / Target | Partial response to information requested on 12 August was sent |
| August 28, 1998 | FDA + Orion + Fermion | Teleconference concerning the CMC questions |
| September 10, 1998 | FDA / S. Al-Habet | Request for additional information, Study 2939057 |
| September 10, 1998 | Orion / Target | Additional information, Study 2939057, was provided |
| September 10, 1998 | Orion / Target | Response to outstanding questions from 12 August |
| September 10, 1998 | Orion / Target | Information requested 18 August was sent to FDA |

| Date | Responsible | Subject |
|--------------------|--------------------|---|
| September 15, 1998 | FDA / R. Tresley | Clarification on daily-on-time calculations |
| September 15, 1998 | FDA / S. Al-Habet | Location of individual information |
| September 16, 1998 | Orion / Target | Phone call to the FDA concerning the individual information requested on 15 September |
| September 18, 1998 | FDA / T. Wheelous | Request to locate information in the pharmacology/toxicology section |
| September 21, 1998 | Orion / Target | Information requested on 15 September was provided |
| September 22, 1998 | Orion / Target | Information requested on 18 September was provided |
| September 25, 1998 | FDA / J. Choudhury | Clarification for the responses submitted on 27 August and on 10 September J. Choudhury requested a telephone conference |
| September 25, 1998 | Orion-Fermion | Fermion submitted the response for additional information requested on August 25, 1998 |
| September 28, 1998 | FDA + Orion | Teleconference corresponding to request on 25 September |
| September 29, 1998 | FDA / M. Sevka | Clarification of coding of laboratory values for study #33 |
| September 29, 1998 | FDA / M. Sevka | Request of glossary of adverse events |
| September 30, 1998 | Orion / Target | Response to coding of laboratory values was provided |
| September 30, 1998 | Orion / Target | Response to August 4, 1998, chemistry comments letter |
| October 1, 1998 | Orion / Target | Individual information requested on 15 September was provided to the FDA |
| October 7, 1998 | Orion / Target | A glossary of adverse events was submitted as requested on 29 September |
| October 13, 1998 | FDA / M. Sevka | Questions regarding the 120-day safety update |
| October 13, 1998 | FDA / S. Al-Habet | Request for individual creatinine clearance values |

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| Date | Responsible | Subject |
|--|---------------------|--|
| October 13, 1998 | FDA / J. Choudhury | Request concerning the unblinding dates |
| October 15, 1998 (October 27, 1998) | Orion / Target | Response provided to the unblinding dates |
| October 20, 1998 | Orion / Target | Response provided to question on 13 October, 120-day safety update |
| October 20, 1998 | FDA / J. Choudhury | Clarification of statistical comments |
| October 22, 1998 | FDA / J. Chouldhury | Clarification of statistical comments |
| October 23, 1998 | FDA + Orion | Teleconference |
| October 23, 1998 | FDA / M. Sevka | Index of case report forms for all Studies was requested |
| October 28, 1998 | Orion / Target | Minutes of the teleconference held on October 23, 1998 was sent to the FDA |
| November 3, 1998 | Orion / Target | Submission of individual creatinine clearance values as requested on October 13, 1998 |
| November 3, 1998 | FDA / J. Chouldhury | Clarification of Statistical Information provided in the NDA |
| November 3, 1998 | FDA / Orion | Teleconference concerning the statistical information requested |
| November 4, 1998 | Orion / Target | Index for case report forms as requested on 23 October was provided |
| November 5, 1998 | FDA/R. Kelley | Clarification: statistical analysis of electronic data and hard copy data in Rat Carcinogenicity Study |
| November 11, 1998 | Orion / Target | Amendment to pending NDA: specifications and test methods for the bulk and packaged drug product |
| November 12, 1998 | Orion / Target | Submission of information requested on November 5, 1998 |
| November 18, 1998 | FDA + Orion | Teleconference concerning safety update |
| November 19, 1998 | FDA / M. Heimann | "CMC" changes to the Package Insert and container labels. |

| Date | Responsible | Subject |
|-------------------|------------------|---|
| November 24, 1998 | Orion / Target | Revised Package Insert and Container Labels provided |
| November 24, 1998 | Orion / Target | Submission of Entacapone labeling to be used in the United Kingdom |
| December 1, 1998 | Orion / Target | Letter of authorization allowing Novartis personnel to contact the agency |
| December 1, 1998 | | Summary of FDA teleconference on November 18, 1998 and submission of information requested during the teleconference |
| December 2, 1998 | Orion / Target | Updated Methods Validation Package The Methods Validation Package is updated to reflect the CMC changes introduced in Orion's CMC submission of September 30, 1998 |
| December 7, 1998 | Orion / Target | Submission of second Safety Update Report |
| December 21, 1998 | FDA / R. Tresley | Data clarification requests |
| December 22, 1998 | Orion / Target | Clarification was provided to Dr. Tresley's request dated December 21, 1998. |
| December 22, 1998 | FDA / R. Tresley | Additional information requested by Dr. Tresley |
| December 31, 1998 | FDA | Approvable Letter |
| January 6, 1999 | Orion / Target | Response to Approvable Letter dated December 31, 1998 |
| January 18, 1999 | Orion / Target | Request for a meeting to discuss the NDA approvable letter |
| January 25, 1999 | Orion / Target | Submission of the proposed logo |
| January 27, 1999 | Orion / Target | Submission of meeting package for discussions related to the NDA approvable letter |
| February 11, 1999 | FDA + Orion | Discussion with FDA related to the approvable |
| February 12, 1999 | FDA / R. Tresley | Request of preclinical toxicological data |
| February 19, 1999 | Orion / Target | Requested preclinical tox data was sent to FDA |

| Date | Responsible | Subject |
|------------------------------------|-------------------|--|
| February 24, 1999 | FDA / T. Wheelous | Results of FDA-meeting regarding approvable letter for Entacapone |
| April 2, 1999 | | Review clock started, FDA received the complete response |
| April 16, 1999 (April 19, 1999) | Orion / Target | Submission of complete response to NDA approvable letter |
| April 22, 1999 | Orion / Target | Additional desk copies requested by FDA were submitted |
| April 28, 1999 | FDA / T. Wheelous | Request for additional desk copy of the complete response |
| April 29, 1999 | FDA / T. Wheelous | Response regarding the reporting of adverse events |
| May 24, 1999 | FDA + Orion | Teleconference regarding complete response to NDA approvable letter |
| May 25, 1999 | Orion / Target | Notification of changes made to the Type II DMF # 12,444 for Entacapone |
| May 26, 1999 | FDA + Orion | Follow up to teleconference regarding complete response to NDA approvable letter |
| May 27, 1999 | FDA | Orion's response was considered a complete class 2 response to FDA's action letter Therefore, the user fee goal date is October 19, 1999. |
| June 4, 1999 | FDA / T. Wheelous | Request by reviewing statistician |
| June 10, 1999 | Orion / Target | Information requested on 4 June was sent to FDA |
| July 2, 1999 | FDA /R. Tresley | Request for additional information |
| July 6, 1999 | FDA / T. Wheelous | Clarification of term requested |
| July 15, 1999 | Orion / Target | Information requested on 2 June was submitted |
| July 16, 1999 | FDA / Kun He | Request to clarify information contained in SAS Data Sets for Celomen study |
| July 21, 1999 | FDA / Kun He | Additional data for Celomen study was requested |

| Date | Responsible | Subject |
|-------------------|------------------------|--|
| July 23, 1999 | FDA / M. Sevka | Request for additional safety information different formulations |
| July 28, 1999 | Orion / Target | Information requested on July 16 and July 21 was sent |
| July 30, 1999 | Orion/Target | Response to questions raised by Dr. Sevka during July 23, concerning formulations was provided |
| August 13, 1999 | FDA / M. Sevka | Questions regarding safety data submitted as part of the complete response |
| August 20, 1999 | FDA / M. Sevka | Questions regarding safety data submitted as part of the complete response |
| September 3, 1999 | FDA / M. Sevka | Additional request for safety information |
| September 9, 1999 | Orion / Target | Response to questions made by Dr. Sevka August 13, August 20, September 3, 1999 |
| October 4, 1999 | Orion / Target | Investigator Financial Disclosure Information |
| October 5, 1999 | Orion / Target | Full waiver for the submission of pediatric use information |
| October 7, 1999 | FDA / T. Wheelous | Draft version of Comtan® labeling from FDA |
| October 8, 1999 | Orion / Target | Revised labeling sent back to FDA |
| October 12, 1999 | FDA + Orion + Novartis | Teleconference concerning the labeling |
| October 12, 1999 | Orion / Target | Final Draft Labeling sent to FDA |
| October 18, 1999 | Orion / Target | Authorization Letter to Novartis Pharmaceuticals |
| October 19, 1999 | FDA | Approval Letter was issued |

XII. ELIGIBILITY OF PATENT FOR EXTENSION

In the opinion of Applicant, the '194 Patent is eligible for an extension of the term for 416 days, and to thus expire on October 19, 2013. The length of the claimed extension of 416 days was determined by Applicant pursuant to 37 C.F.R. § 1.775, to be fourteen (14) years from the date of the FDA final approval, as described below:

A. Length of the Regulatory Review Period (37 C.F.R. § 1.775(c))

1. *Period Pursuant to Paragraph (c)(1)*

The period defined at 37 C.F.R. § 1.775(c)(1) began on November 29, 1991 (the date the IND became effective) and ended on January 2, 1998 (the date the NDA was filed). The (c)(1) period is thus 2,227 days.

2. *Period Pursuant to Paragraph (c)(2)*

The period defined at 37 C.F.R. § 1.775(c)(2) began on January 2, 1998 (the date the NDA was submitted pursuant to Section 505(b) of the FFDCA) and ended October 19, 1999 (the commercial marketing and use approval date). The (c)(2) period is thus 656 days.

The total (c)(1) and (c)(2) time period is thus 2,883 days.

B. Term of the Patent as Extended (37 C.F.R. § 1.775(d))

The term of the '194 Patent, as extended, was then calculated to expire on October 19, 2013, pursuant to 37 C.F.R. § 1.775(d).

1. *(d)(1) Period (Days Subtracted from Regulatory Review Period)*

The regulatory review period upon which the period of extension is calculated by subtracting, from the regulatory review period as determined in (c)(1) and (c)(2) of this section, the following:

- (i) *The number of days in the periods of paragraphs (c)(1) and (c)(2) above which were on or before August 29, 1995, the issue date of the original patent.*

The number of days in the period of the IND, effective on November 29, 1991, which were on or before August 29, 1995, the date the '194 Patent issued, is a period of 1,369 days. Therefore, 1,369 days are deducted from 2,227 days to equal 858 days.

The number of days in the period of the NDA, with the initial submission of NDA 20-796 on January 2, 1998, and approval on October 19, 1999, which were on or before August 29, 1995, the date the '194 Patent was issued, is a period of 0 days. Thus, 0 days are deducted to equal 656 days.

The total number of days after deduction is 1,514.

- (ii) *The number of days in the periods of paragraphs (c)(1) and (c)(2) during which the Applicant did not act with due diligence.*

In the Applicant's opinion, marketing applicant acted with due diligence as defined at 35 U.S.C. § 156(d)(3) during the above calculated periods of paragraphs (c)(1) and (c)(2). Accordingly, zero days are subtracted from the regulatory review period.

- (iii) *One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section (ignoring half days).*

There are 2,227 days in the period defined by paragraph (c)(1). The total deduction from 2,227 days pursuant to paragraphs (d)(1)(i) and (ii) of this section are 1,369, which equals 858 days. One half of 2,227 days, ignoring half days for purposes of subtraction, is 1,113.5 days. Subtracting 1,113.5 days from 2,883 results in a time period of 1,769.5 days.

Thus, the period determined according to paragraph (d)(1) is 1,769 days.

2. *(d)(2) Date*

The number of days determined in paragraph (d)(1), 1,769 days, added to the original term of the patent, *i.e.*, 17 years from the issue date (August 29, 1995), results in an extended patent expiration date of July 3, 2017.

3. *(d)(3) Date*

Fourteen years added to the October 19, 1999, the date of approval under the Federal Food, Drug and Cosmetic Act, yields an extended patent expiration date of October 19, 2013.

4. *(d)(4) Date*

Comparing the extended terms determined according to paragraphs (d)(2) and (d)(3), the earlier date is October 19, 2013.

5. *(d)(5) Date*

The original patent issued after September 24, 1984. Five years added to the original expiration date (August 29, 2012) of the patent is August 29, 2017.

By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other, the earlier date is October 19, 2013.

6. *(d)(6) Date*

The original patent was issued after September 24, 1984. Thus, this section thus does not apply.

XIII. ACKNOWLEDGMENT OF DUTY TO DISCLOSE

Applicant hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is

material to the determination of entitlement to the term extension sought pursuant to 37 C.F.R. § 1.765.

XIV. APPLICATION FEE

Applicant submits herewith a check for \$1,120.00 in payment of the fee set forth at 37 C.F.R. § 1.20(j).

The Commissioner is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment to Deposit Account No. 02-4800.

XV. CORRESPONDENCE ADDRESS

Please direct all correspondence and inquiries regarding this matter to:

Teresa Stanek Rea
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404
Tel: (703) 836-6620

XVI. DUPLICATE OF APPLICATION AND CERTIFICATION

Applicant encloses herewith a copy of the present application papers, and certifies that said copy is a duplicate of the application papers. For the convenience of the Senior Legal Advisor of the Patent Office, Applicant is also enclosing three (3) additional copies of the application.

XVII. DECLARATION

A Declaration pursuant to 37 C.F.R. § 1.740(b) is attached hereto.

Patent No. 5,446,194
Application No. 08/121,617
Attorney's Docket No. 020325-053

In view of the foregoing, an extension of the term of the above-identified patent respectfully is requested.

Respectfully submitted

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: December 17, 1999

By: 

Teresa Stanek Rea
Registration No. 30,427

Post Office Box 1404
Alexandria, VA 22313-1404
Tel: (703) 836-6620

EXHIBIT 1



NDA 20-796

Food and Drug Administration
Rockville MD 20857

Orion Corporation
Attention: Robert Mc Cormack, Ph.D.
Vice-President, Regulatory Affairs
Target Research Associates
1801 East Second Street
Scotch Plains, N. J. 07076

OCT 19 1999

Dear Dr. McCormack:

Please refer to your new drug application (NDA) dated October 24, 1997, received January 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Comtan (entacapone) Tablets 200 mg.

We acknowledge receipt of your submissions dated:

April 16, 1999

May 24, 1999

May 25, 1999

July 15, 1999

July 28, 1999

July 30, 1999

September 9, 1999

October 5, 1999

Your submission of April 16, 1999 constituted a complete response to our December 31, 1998 action letter.

This new drug application provides for the use of Comtan (entacapone) 200 mg tablets as an adjunct to levodopa / carbidopa to treat patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off" (so-called "fluctuating" patients).

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter. In particular, this approval applies to formulation 55.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-796." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated April 16, 1999 as requested in our December 31, 1998 action letter. This commitment is described below.

Pharmacology / Toxicology

We do not agree that you have provided evidence for saturation of absorption at doses of 100 mg/kg or higher in the mouse carcinogenicity study, and you have not demonstrated in a 3-month study that 100 mg/kg is approximately one half the maximum tolerated dose. As you have therefore failed to validate the existing study, it will be necessary for you to conduct a mouse carcinogenicity study during Phase 4. This study may be a repeat of the mouse bioassay or an alternative study such as the mouse p53 assay. If you choose an alternative mouse model, your justification for the choice and a protocol should be submitted for evaluation by the Executive Carcinogenicity Assessment Committee (ECAC). We also recommend that, if you choose to repeat the bioassay, you seek concurrence for dose selection from the ECAC. The dose selection studies should be initiated immediately, and the completed studies should be submitted as soon as possible.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. As an IND will not be required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632).

We note that in your October 5, 1999 submission, received October 6, 1999, you request a waiver of the pediatric study requirement in accordance with the provisions of 21 CFR 314. We will notify you within 120 days of receipt of your submission, February 3, 2000, whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. In the event that we deny your request for a waiver of the pediatric study requirements and, therefore, conclude that you must perform studies in (a subset of) the pediatric population, you may wish to qualify for pediatric exclusivity. In that case you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. If we do deny your waiver request, we recommend that you submit a Proposed Pediatric Study Request within 120 days from the date that we inform you of this denial. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

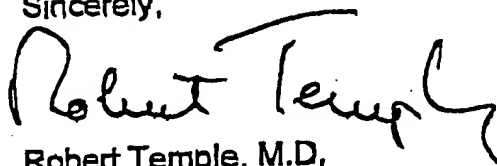
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 20-796

Page 4

If you have any questions, contact Teresa Wheelous, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

A handwritten signature in black ink, appearing to read "Robert Temple". The signature is fluid and cursive, with a large, sweeping initial "R" and a long, horizontal stroke extending to the right.

Robert Temple, M.D.

Director

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Enclosure

EXHIBIT 2

Assignment of Application for Patent

Valtuutetut: Reijo Johannes Backstrom, Kalevi Evert Heinola, Erkki Juhani

Honkaniemi, Seppo Kalevi Kaakkola, Pekka Juhani Kairisalo, Inge-Britt Yvonne
Linden, Pekka Iopias Mannisto, Erkki Aarne Olavi Mäntinen, Pentti Pöhto,
Aino Kyllikki Pippuri

NEW PHARMACOLOGICALLY ACTIVE COMPOUNDS, METHODS FOR THE
PREPARATION THEREOF AND COMPOSITIONS CONTAINING SAME

Letters Patent of the United States of America:

And Whereas, Osion-yhcvma Oy

of Espoo, Finland

is desirous of acquiring an interest therein and in the
r from the United States;

Now Therefore, be it known by all whom it may concern, that for and in consideration of ONE Dollars (\$1.00) and other valuable consideration to US in hand paid, the receipt of which is hereby acknowledged we have assigned, sold, and set over, and by these presents do assign, sell, and set over unto the said Orion-yhtymä Oy

* the entire rights, title, and interest in and to the said invention, as fully set forth and described in the specification prepared and executed by US on Nov. 16, 1987 19.....
dated 19 serial No preparatory to

obtaining Letters Patent therefor; said invention, application and Letters Patent to be held and enjoyed by the said Orion Yhtymä Oy for its own use and behoof, and for the use and behoof of its successors, assigns and legal representatives to the full end of the term for which said Letters Patent are granted, as fully and entirely as the same would have been held by us had this assignment and sale not been made.

In Testimony Whereof, _____ We hereunto set our _____ hands and affix our
seals at _____ Espoo, Finland _____ State of _____
this 16th day of November A. D. 19 87

Signed, sealed and delivered in the presence of—

7 - 12 - 1921
Sgt. K. K. K.

Signatures of Witnesses

1. Was ist das?
 2. Welche Funktion hat es?
 3. Wie wird es hergestellt?
 4. Woher kommt es?
 5. Wie wird es verwendet?
 6. Welche Eigenschaften hat es?
 7. Welche Gefahren sind mit dem Umgang verbunden?
 8. Welche Entsorgungsmöglichkeiten gibt es?
 9. Welche weiteren Informationen sind relevant?
 10. Welche weiteren Fragen sind zu klären?

Signature(s) of Inventor(s):

2 Fullerton - F. to F. to

3 Edi. Davis

4 James Smith

10 Alvin Pappas

11 James Pappas

TEL 4820 RA6520

RECORDED
PATENT & TRADEMARK OFFICE

NOV 27 1987

Handwritten signature
OFFICE OF THE
COMMISSIONER OF PATENTS

EXHIBIT 3

United States Patent [19]
Bäckström et al.

US005446194A

[11] Patent Number: 5,446,194
[45] Date of Patent: Aug. 29, 1995

[54] PHARMACOLOGICALLY ACTIVE
CATECHOL DERIVATIVES

[75] Inventors: Reijo J. Bäckström, Helsinki; Kalevi E. Heinola, Järvempää; Erkki J. Honkanen, Vantaa; Seppo K. Kaakkola, Helsinki; Pekka J. Kairisalo, Helsinki; Inge-Britt Y. Linden, Helsinki; Pekka I. Männistö, Helsinki; Erkki A. O. Nissinen, Espoo; Pentti Pohto, Helsinki; Aino K. Pippuri; Jarmo J. Pystynen, both of Espoo, all of Finland

[73] Assignee: Orion-yhtymä Oy, Espoo, Finland

[21] Appl. No.: 121,617

[22] Filed: Sep. 16, 1993

Related U.S. Application Data

[60] Division of Ser. No. 987,245, Dec. 7, 1992, Pat. No. 5,283,352, which is a continuation of Ser. No. 792,655, Nov. 15, 1991, abandoned, which is a division of Ser. No. 587,791, Sep. 25, 1990, Pat. No. 5,112,861, which is a division of Ser. No. 126,911, Nov. 27, 1987, Pat. No. 4,963,590.

[30] Foreign Application Priority Data

Nov. 28, 1986 [FI] Finland 864875
May 27, 1987 [GB] United Kingdom 8712437

[51] Int. Cl.⁶ C07C 205/22; C07C 255/50

[52] U.S. Cl. 558/401; 558/404;
558/414; 564/166; 564/167; 564/169; 560/136

[58] Field of Search 558/401, 404, 414;
564/166, 167, 169; 560/136

[56] References Cited

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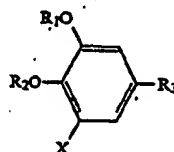
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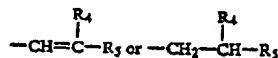
Primary Examiner—Jacqueline Haley
Attorney, Agent, or Firm—Burns, Doane, Swecker & Mathis

[57] ABSTRACT

A compound according to formula 1



wherein R₁ and R₂ independently represent hydrogen, carbamoyl which is substituted by an alkyl of 1 to 4 carbon atoms, alkylcarbonyl of 2 to 5 carbon atoms or phenyl carbonyl, X represents halogen nitro or cyano and R₃ represents



wherein R₄ represents cyano or alkylcarbonyl of 2 to 5 carbon atoms and R₅ represents carbamoyl which is unsubstituted or substituted with alkyl of 1 to 8 carbon atoms or which is substituted with hydroxyalkyl of 1 to 8 carbon atoms or pharmaceutically acceptable esters and salts thereof, and a pharmaceutically acceptable carrier therefor, as well as pharmaceutical compositions containing said compounds as COMT inhibitors.

4 Claims, 2 Drawing Sheets

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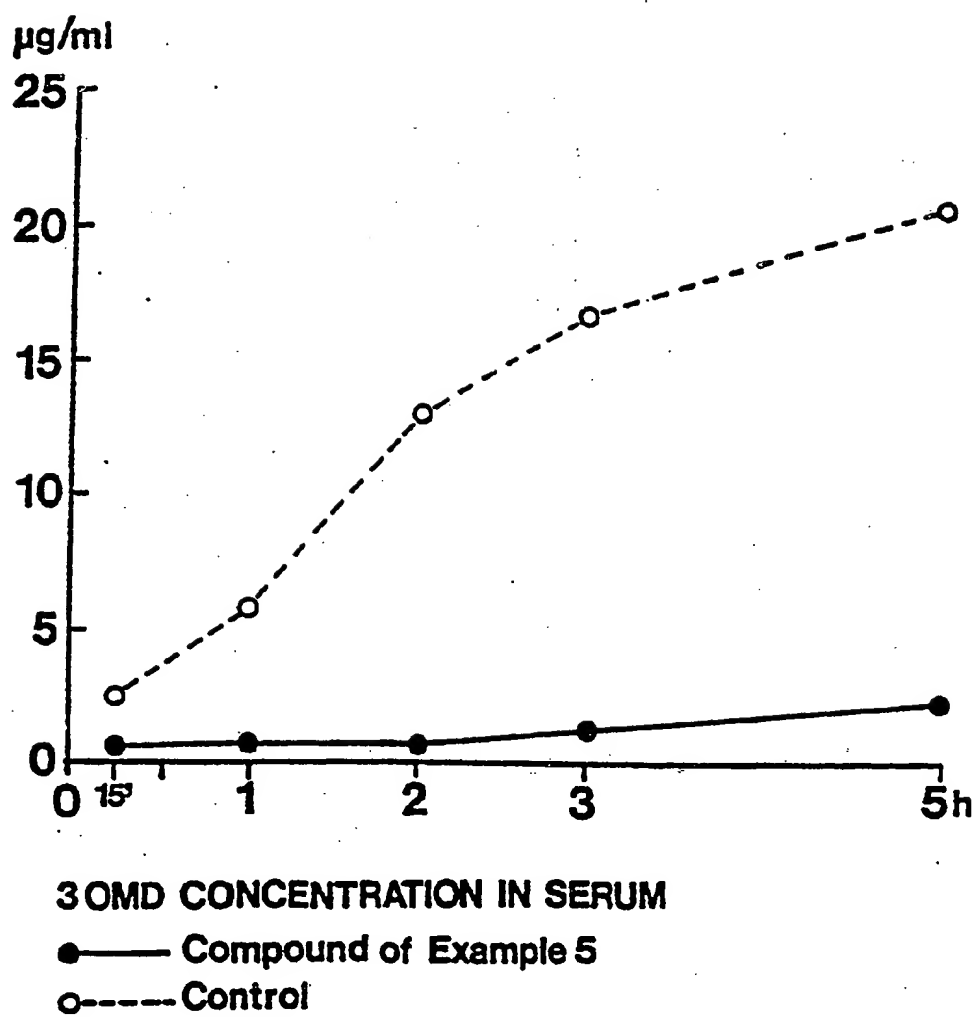
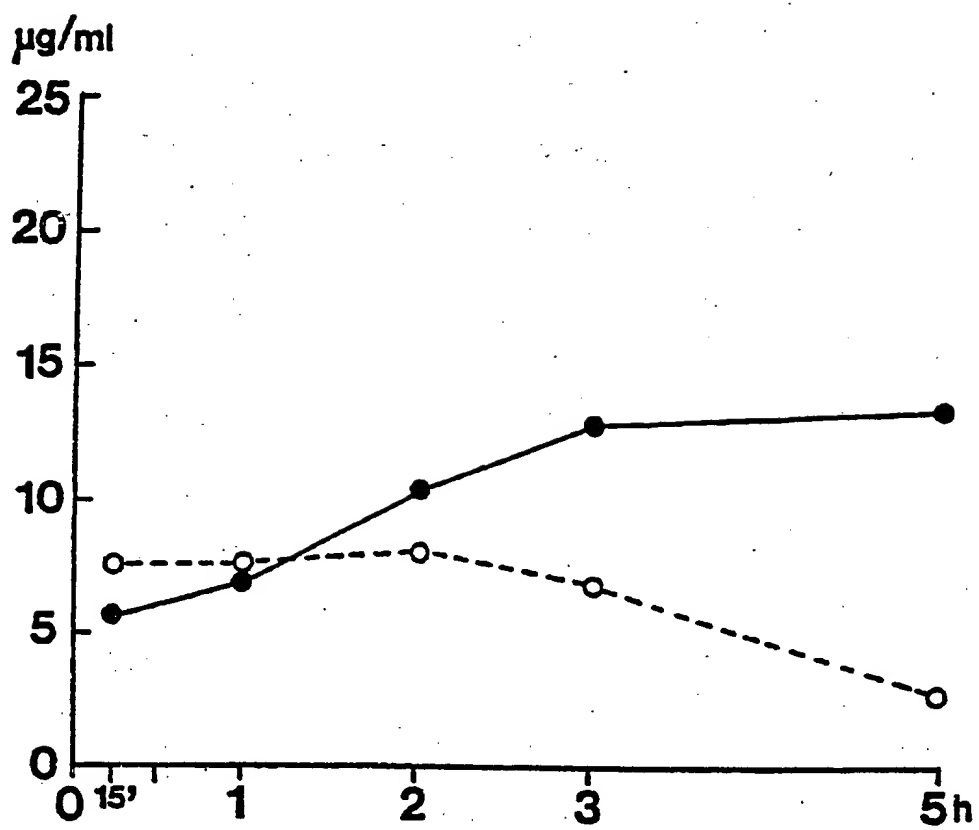
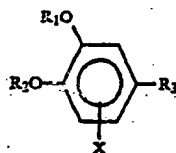


Fig. 1

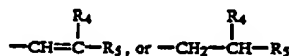
**L-DOPA CONCENTRATION IN SERUM****●— Compound of Example 5****○--- Control****Fig. 2**

PHARMACOLOGICALLY ACTIVE CATECHOL DERIVATIVES

This application is a divisional of Application Ser. No. 07/987,245, filed Dec. 7, 1992, now U.S. Pat. No. 5,283,352, which is a continuation of Application Ser. No. 07/792,655, filed Nov. 13, 1991, now abandoned, which is a divisional of application Ser. No. 07/587,791, filed Sep. 25, 1990, now U.S. Pat. No. 5,112,861, which is a divisional of application Ser. No. 07/126,911, filed Nov. 27, 1987, now U.S. Pat. No. 4,963,590. The present invention relates to new pharmacologically active catechol derivatives according to formula I



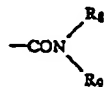
wherein R₁ and R₂ independently comprise hydrogen, alkyl, optionally substituted acyl or optionally substituted aroyl, lower alkylsulfonyl or alkylcarbamoyl or taken together form a lower alkylidene or cycloalkylidene group, X comprises electronegative substituent such as halogen, nitro, cyano, lower alkylsulfonyl, sulfonamido, trifluoromethyl, aldehyde or carboxyl and R₃ comprises hydrogen, halogen, substituted alkyl, hydroxyalkyl, nitro, cyano, optionally substituted amino, trifluoromethyl, lower alkylsulfonyl, sulfonamide, aldehyde, alkylcarbonyl, aralkylidenecarbonyl or carboxyl group or a group selected from



wherein R₄ comprises hydrogen, alkyl, amino, cyano, carboxyl or acyl and R₅ comprises hydrogen, amino, cyano, carboxyl, alkoxycarbonyl, carboxyalkenyl, nitro, acyl, hydroxyalkyl, carboxyalkyl, COZ, wherein Z is an optionally substituted heterocyclic ring or one of the following optionally substituted groups; carboramido, carbamoyl, aroyl or heteroaryl or R₄ and R₅ together form a five to seven membered substituted cycloalkane ring;



wherein n is 0-1, m is 0-7 and R comprises alkyl, hydroxy, carboxyalkyl, optionally substituted alkene, optionally substituted heterocyclic ring, alkoxy or substituted amino;



wherein R₈ and R₉ independently comprise hydrogen or one of the following optionally substituted groups; alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl or taken together form an optionally substituted piperidyl group;



wherein R₁₀ comprises a substituted alkyl group.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the 3-LMD serum concentrations for the new compound and for a control compound which does not contain a COMT inhibitor.

FIG. 2 shows the levodopa serum concentrations after the same treatments.

The term "alkyl" as employed herein by itself or as part of another group includes both straight and branched chain radicals of up to 18 carbon atoms, preferably 1 to 8 carbon atoms, most preferably 1 to 4 carbon atoms. The term "lower alkyl" as employed herein by itself or as part of another group includes both straight and branched chain radicals of 1 to 7, preferably 1 to 4, most preferably 1 or 2 carbon atoms. Specific examples for the alkyl and lower alkyl residues, respectively, are methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, pentyl, hexyl, octyl, decyl and dodecyl including the various branched chain isomers thereof.

The term "alkenyl" and "alkynyl" designate a hydrocarbon residue as defined above with respect to the term "alkyl" including at least one carbon to carbon double bond and carbon to carbon triple bond, respectively. The alkenyl and alkynyl residues may contain up to 12, preferably 1 to 8, most preferably 1 to 4 carbon atoms.

The term "acyl" as employed herein by itself or as part of another group refers to an alkylcarbonyl or alkenylcarbonyl group, the alkyl and alkenyl groups being defined above.

The term "aroyl" as used herein by itself or as part of another group refers to an arylcarbonyl group, the aryl group being a monocyclic or bicyclic group containing from 6 to 10 carbon atoms in the ring portion. Specific examples for aryl groups are phenyl, naphthyl and the like.

The term "lower alkylidene" refers to a chain containing from 2 to 8, preferably 2 to 4 carbon atoms. In a similar way the term "cycloalkylidene" refers to a cyclic hydrocarbon group containing 3 to 8, preferably 5 to 7 carbon atoms.

The term "alkoxy" as employed herein by itself or as part of another group includes an alkyl residue as defined above linked to an oxygen atom.

The term "cycloalkyl" includes saturated cyclic hydrocarbon groups containing 3 to 8, preferably 5 to 7 carbon atoms. Specific examples are the cyclopentyl, cyclohexyl, cycloheptyl and adamantyl groups.

The term "aralkyl" as employed herein refers to alkyl groups as defined above having an aryl substituent. A specific example is the benzyl group.

The term "halogen" as used herein refers to chlorine, bromine, fluorine or iodine, chlorine and bromine being preferred.

The term "optionally substituted" as used herein in connection with various residues refers to halogen substituents, such as fluorine, chlorine, bromine, iodine or trifluoromethyl groups, alkoxy, aryl, alkyl-aryl, halogen-aryl, cycloalkyl, alkylcycloalkyl, hydroxy, alkyl-amino, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, or alkylthio substituents.

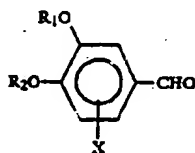
The "optionally substituted" groups may contain 1 to 3, preferably 1 or 2, most preferably 1 of the above mentioned substituents.

The term "heteroaroyl" or "heteroaryl" or "heteroalkyl" as employed herein refers to monocyclic or bicyclic

clic group containing 1 to 3, preferably 1 or 2 heteroatoms N and/or O and/or S. Specific examples are morpholinyl, piperidyl, piperidinyl, piperazinyl, pyridyl, pyrrollyl, quinolinyl and quinolyl.

The invention also relates to pharmaceutically acceptable salts of the present compounds.

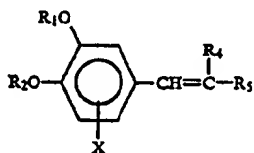
The present invention also relates to methods for the preparation of compounds of formula I. In accordance with the present invention compounds of formula I may be prepared for instance so, that an aldehyde of formula II



wherein R₁, R₂ and X are as defined above, is condensed in a base or acid catalyzed reaction with a compound of formula III



having an active methyl or methylene group and wherein R₄ and R₅ are as defined above, giving the compounds of formula Ia



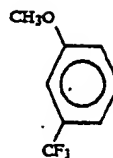
wherein R₄ and R₅ are as defined above and wherefrom the double bond optionally may be reduced to a single bond.

The compounds according to formula II are also, in addition to being valuable medicines according to the present invention, new valuable intermediates for preparing other valuable products according to the invention.

Compounds of formula II wherein x is a cyano group can be prepared from the corresponding compounds, wherein X is halogen, preferably bromine, by allowing these compounds to react with cuprous cyanide in a polar, aprotic solvent, such as pyridine, N-methylpyrrolidone or N,N-dialkylformamide at elevated temperature (100°-200° C.).

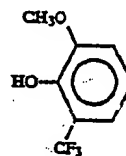
Alternatively the compounds of formula II, wherein X is a 5-cyano group can be prepared by formylation of 2,3-dihydroxybenzonitrile with hexamethylenetetramine.

Compounds of formula II, wherein X is 5-trifluoromethyl can be prepared starting from 3-methoxytrifluoromethylbenzene of formula XIV



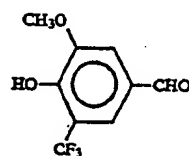
XIV

which compound is treated first with butyllithium and then with trimethylborate and further with performic acid to give the compound of formula XV



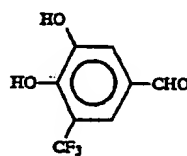
XV

which compound is formylated with hexamethylenetetramine in trifluoroacetic acid to give a compound of formula XVI



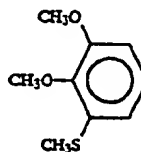
XVI

which compound is, if desired, demethylated for example with boron tribromide to give the compound of formula XVII



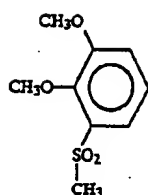
XVII

Compounds of formula II, wherein X comprises a 5-methylsulfonyl group, can be prepared from 2,3-dimethoxythioanisole of the formula XVIII

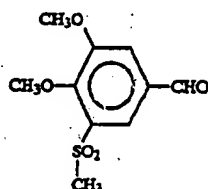


XVIII

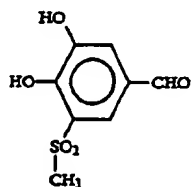
which compound is treated first for example with peroxyacetic acid to give the corresponding sulfone of formula XIX



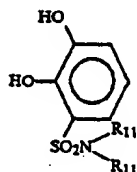
which compound is then formylated with hexamethylenetetramine in trifluoroacetic acid to give the compound of formula XX



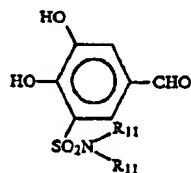
which compound may be, if desired, demethylated (HSr or SBr₃) to give a compound of formula XXI



The compound of formula II, wherein X comprises sulfonamido, can be prepared by formylation of 2,3-dihydroxybenzenesulfonamide of formula XXII



wherein R₁₁ means hydrogen or alkyl, to give the compound of formula XXIII



Alternatively compounds of formula I according to the present invention can be prepared from a ketone of formula IV

XIX

5

10

15

XX

20

25

XXI 30

35

40

XXII 45

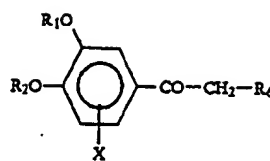
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55

XXIII

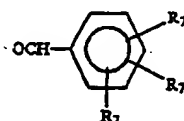
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65



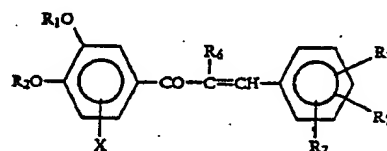
IV

wherein R₁, R₂, X are as defined above and R₆ comprises hydrogen or alkyl, by a condensation with an aldehyde of formula V



V

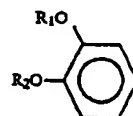
wherein R₇ comprises hydrogen, alkyl, alkoxy or dialkylamino to give the compounds of formula Ib



Ib

wherein R₁, R₂, X, R₆ and R₇ are as defined above.

Alternatively compounds of formula I, wherein R₃ comprises a substituted alkyl group can be prepared by Friedel-Craft's reaction from a compound of formula VI



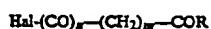
VI

wherein R₁ and R₂ are as defined above by allowing the compound of the formula VI to react in the presence of aluminium chloride either with a cyclic acid anhydride of formula VII



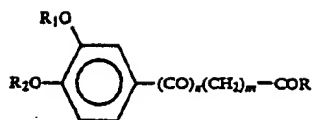
VII

wherein m is 1-7 or alternatively with a dicarboxylic acid ester chloride of formula VIII

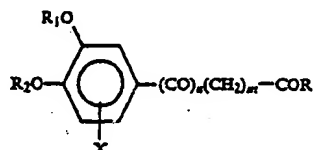


VIII

wherein m is 0-7 and n is 0-1 and R is as defined above and Hal is a halogen atom, to give the compounds of formula IX

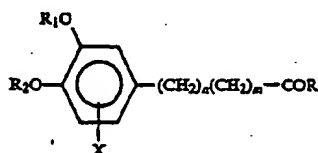


wherein the aromatic ring will be substituted with the group X to give the compounds of formula Ic

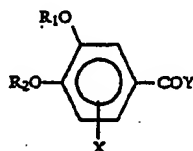


wherein R, R₁, R₂ and X are as defined above.

In the compounds of formula Ic the carbonyl group can be reduced to a methylene group by conventional methods (Clemmensen and Wolff-Kischner reduction) to give compounds of formula Id



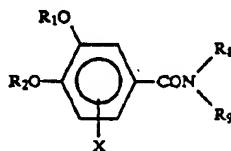
The compounds according to the present invention, wherein R₃ comprises a substituted carbamido group, can be prepared by allowing an activated benzoic acid derivative of formula X



wherein R₁, R₂ and X are as defined above and Y comprises halogen or some other activated group to react with an amine of formula XI



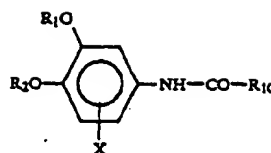
wherein R₈ and R₉ are as defined above to give compounds of formula Ic



wherein R₁, R₂, X, R₈ and R₉ are as defined above.

The compounds of formula I, wherein R₃ is an acylated amino group having formula If

IX



If

5

10

Ic

15

20

Id

25

30

X

40

45

XI

50

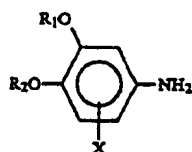
55

Ic

60

65

wherein R₁, R₂, X and R₁₀ are as defined above can be prepared by allowing an aniline derivative of formula XII



XII

wherein R₁, R₂ and X are as defined above, to react with an activated carboxylic acid derivative of formula XIII



XIII

wherein Y and R₁₀ are as defined above.

The invention relates to compositions where the compounds of formula I may be used as the active medicine. The compositions may contain the compounds of formula I alone or combined with some other medicines. For the treatment of Parkinson's disease the compounds according to formula I are given with levodopa, each in its own composition or combined in one composition. Also peripheral dopa decarboxylase (DDC) inhibitors, such as carbidopa or benserazide may be present, even though they are not obligatory.

The compounds according to this invention may be given in different dosage forms for administering in any suitable enteral or parenteral way. The dosage forms, like tablets, pills, injection liquids etc may be manufactured by the known principles in the art. One can use any pharmaceutically accepted additives, lubricants, fillers etc to modify different properties of the dosage forms.

Catechol-O-methyltransferase (COMT) catalyzes the transfer of the methyl group from S-adenosyl-L-methionine to a number of compounds with catechol structures. This enzyme is important in the extraneuronal inactivation of catecholamines and drugs with catechol structures. COMT is one of the most important enzymes involved in the metabolism of catecholamines. It is present in most tissues, both in the periphery and the central nervous system. The highest activities are found in the liver, intestine and kidney. COMT probably is present in soluble and membrane bound forms. The exact character of the two forms has not been established.

In Parkinson's disease the dopaminergic neurones, primarily the nigrostriatal neurones, are damaged, causing dopamine deficiency in the cerebral basal ganglia. This deficiency can be compensated by levodopa which is converted to dopamine in the central nervous system under the influence of DDC.

Today, levodopa treatment is almost invariably supplemented with a peripheral DDC inhibitor to inhibit too early dopamine formation and thereby to increase

the cerebral levodopa concentration and to decrease the peripheral side effects of dopamine.

In addition to DDC, COMT metabolizes levodopa, converting it to 3-O-methyldopa (3-OMD). 3-OMD readily penetrates the blood-brain barrier via an active transport system. Alone it is therapeutically ineffective and detrimental when competing with levodopa. 3-OMD is accumulated in tissues because of its long half-life (ca. 15 h) compared to levodopa (ca. 1 h). The high activity of COMT clearly correlates with the poor efficacy of levodopa despite the presence of peripheral DDC inhibitor.

In addition to monoamine oxidase (MAO), COMT is a major enzyme participating in the amine metabolism. By inhibiting the metabolism of endogenous amines (dopamine, noradrenaline, adrenaline) in the brain the COMT inhibitors decrease decomposition of these compounds. Thus they may be useful in the treatment of depression.

By inhibiting peripheral COMT effectively, COMT inhibitors direct the metabolic route of levodopa towards decarboxylation, forming thereby more dopamine which is important in the treatment of hypertension and heart failure.

It has been unexpectedly observed that the compounds according to the invention are extremely effective COMT inhibitors. They open up new, previously unknown possibilities in the treatment of Parkinson's disease. In addition the new compounds may be useful also in the treatment of depression and heart failure as well as hypertension.

The new COMT inhibitors, which inhibit formation of 3-OMD, may decrease the adverse effects of long-term use of levodopa. Furthermore, levodopa doses can be reduced. It has been shown that the dose of levodopa can be reduced by half or to one-third of the dose used without COMT inhibitor. Since dosage of levodopa is individual, it is difficult to give any absolute dosage, but daily doses as low as 25-50 mg have been considered sufficient to start with.

A preliminary clinical trial on n-butyl gallate, a known COMT inhibitor, showed patients with Parkinson's disease clearly to benefit of n-butyl gallate. The study was, however, discontinued because of the too high toxicity of n-butyl gallate.

The COMT inhibitory efficacy of the compounds according to the invention was tested using the following experimental procedures.

Determination of COMT activity in vitro

The in vitro activity of COMT was determined in enzyme preparations isolated from the brain and liver of female Han:WIST rats, weight ca. 100 g. The rats were killed by carbon dioxide, and the tissues were removed and stored at -80° C. until determination of enzyme activity.

The enzyme preparation was prepared by homogenizing the tissues in 10 mM phosphate buffer, pH 7.4, (1:10 weight g/ml) which contained 0.3 mM dithiothreitol. The homogenate was centrifuged 15000 x G for 20 min. The supernatant was recentrifuged 100000 x G for 60 min. All procedures were done at +4° C. The supernatant of the last centrifugation (100000 x G) was used to determine the activity of soluble COMT enzyme.

Determination of IC₅₀ was performed by measuring the COMT activity in several drug concentrations of the reaction mixture which contained the enzyme prep-

aration, 0.4 mM dihydroxybenzoic acid (substrate), 5 mM magnesium chloride, 0.2 mM S-adenosyl-L-methionine and COMT inhibitor in 0.1 M phosphate buffer, pH 7.4. No COMT inhibitor was added to the control. The mixture was incubated for 30 min at 37° C. whereafter the reaction was stopped by perchloric acid and the precipitated proteins were removed by centrifugation (4000 x G for 10 min). The activity of the enzyme was measured by determining the concentration of 3-methoxy-4-hydroxybenzoic acid formed from the substrate of COMT (dihydroxybenzoic acid) by HPLC using an electrochemical detector. Chromatography was performed by injecting 20 µl of the sample in a 4.6 mm x 150 mm Spherisorb ODS column (particle size 5 µm). The reaction products were eluted from the column with 20% methanol containing 0.1 M phosphate, 20 mM citric acid and 0.15 mM EDTA, pH 3.2, at a flow rate of 1.5 ml/min. The electrochemical detector was set to 0.9 V against an Ag/AgCl electrode. The concentration of the reaction product, 3-methoxy-4-hydroxybenzoic acid, was compared with the control samples and the samples containing COMT inhibitor. The IC₅₀ value is the concentration which causes a 50% decrease in COMT activity.

Effect of COMT inhibitors in vivo

Male Han:WIST rats, weight 200-250 g, were used in the experiment. The control group was given 50 mg/kg carbidopa 30 min before levodopa (50 mg/kg). The test group was also given carbidopa 50 mg/kg 30 min before levodopa + COMT inhibitor. The drugs were administered orally.

Sampling

About 0.5 ml of blood was drawn from the tail artery. The sample was allowed to coagulate in ice. Thereafter the sample was centrifuged and serum separated. Serum was stored at -80° C. until determination of concentrations of levodopa and its metabolite 3-OMD.

Determination of levodopa and 3-OMD serum concentrations

To serum (e.g. 100 µl), an equal volume of 0.4 M perchloric acid, 0.1% sodium sulphate, 0.01% EDTA, which contained dihydroxybenzylamine as internal standard, were added. The sample was mixed and kept in ice, whereafter the proteins were removed by centrifugation (4000 x G for 10 min.) and the concentrations of levodopa and 3-OMD were determined by HPLC using an electrochemical detector. The compounds were separated in a 4.6 mm x 150 mm Ultrasphere ODS column in an eluent containing 4% acetonitrile, 0.1 M phosphate buffer, 20 mM citric acid, 0.15 mM EDTA, 2 mM octylsulphonic acid and 0.2% tetrahydrofuran, pH 2.8. The flow rate was 2 ml/min. The electrochemical detector was set to +0.8 V against an Ag/AgCl electrode. The concentrations of the test compounds were determined by comparing the heights of the peaks with that of the internal standard. The ratio was used to calculate the serum concentrations of levodopa and 3-OMD in control rats and those given COMT inhibitor.

Results

The best COMT inhibitors according to the invention were more than thousand times more potent in vitro than the most potent known reference compound U-0521 (Table I). Also the orally administered COMT

inhibitors were shown to inhibit the formation of serum 3-OMD significantly more than U-0521 (Table II). The reference compound U-0521 furthermore penetrated the blood-brain barrier and inhibited the tyrosine hydroxylase activity thereby blocking the biosynthesis of vitally important catecholamines. In contrast the com-

pounds according to the invention are COMT specific and they do not significantly penetrate the blood-brain barrier.

Results in vitro

TABLE I

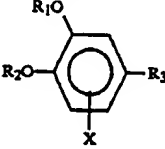
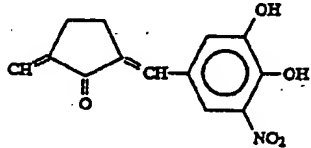
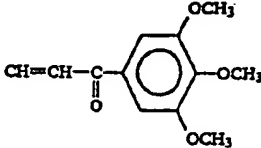
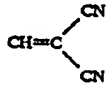


|  | | | | | COMT-INHIBITION IN BRAIN TISSUE (IC50 μM) |
|---|----------------|----------------|-------------------|--|---|
| Example compound | R ₁ | R ₂ | X | R ₃ | |
| 79 | H | H | 3-NO ₂ |  | 3 |
| 11 | H | H | 3-NO ₂ |  | 5 |
| 8 | H | H | 3-NO ₂ | $\text{CH}=\text{CH}-\text{C}(=\text{O})-\text{H}$ | 6 |
| 6 | H | H | 3-NO ₂ | $\text{CH}=\text{C}(\text{CH}_3)-\text{C}(=\text{O})-\text{CH}_3$ | 12 |
| 110 | H | H | 3-NO ₂ | NO ₂ | 12 |
| 109 | H | H | 3-NO ₂ | $\text{O}=\text{C}-\text{CH}_3$ | 16 |
| 130 | H | H | 3-NO ₂ | NO ₂ | 18 |
| 5 | H | H | 3-NO ₂ |  | 20 |
| 27 | H | H | 3-NO ₂ |  | 20 |
| 16 | H | H | 3-NO ₂ | $\text{CH}=\text{C}(\text{CH}_3)-\text{CH}(\text{OH})-\text{CH}_3$ | 23 |
| 111 | H | H | 3-NO ₂ | $\text{O}=\text{C}-\text{H}$ | 24 |
| 113 | H | H | 3-NO ₂ | -Cl | 25 |
| 112 | H | H | 3-NO ₂ | -CN | 30 |
| 28 | H | H | 3-NO ₂ |  | 27 |

TABLE 1-continued

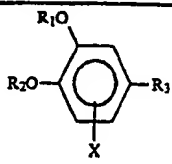





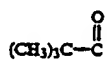
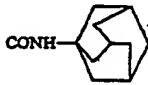
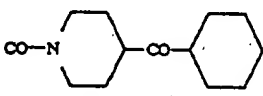
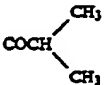
| Example compound |  | | | | COMT-INHIBITION IN BRAIN TISSUE (IC50(nM)) |
|------------------|---|---|-------------------|---|--|
| | R ₁ | R ₂ | X | R ₃ | |
| 26 | H | H | 3-NO ₂ |  | 33 |
| 3 | H | H | 3-NO ₂ | CH=CH-COOH | 37 |
| 128 |  |  | 3-NO ₂ | NO ₂ | 60 |
| 127 |  |  | 3-NO ₂ | 75 | |
| 24 | H | H | 3-NO ₂ | CH ₂ CH ₂ CH ₂ CH ₂ COOH | 90 |
| 109 | H | H | 3-NO ₂ | -H | 140 |
| 131 |  | H | 3-NO ₂ | NO ₂ | 220 |
| 41 | H | H | 6-NO ₂ | CH ₂ CH ₂ CH ₂ CH ₂ COOH | 380 |
| 34 | H | H | 3-Cl |  | 400 |
| 67 | CH ₃ CO | CH ₃ CO | 6-NO ₂ |  | 750 |
| U-0521 | H | H | 3-H |  | 6000 |

TABLE 2

| Oral dose | Compound | In vivo results 3-OMD concentration % of control | |
|-----------|-------------|--|-----|
| | | 1 h | 5 h |
| 3 mg/kg | Example 110 | -97 | -80 |
| 4.3 mg/kg | Example 127 | -67 | -76 |
| 4.7 mg/kg | Example 128 | -70 | -77 |
| 4.3 mg/kg | Example 131 | -92 | -83 |
| 4.1 mg/kg | Example 130 | -98 | -92 |
| 30 mg/kg | Example 19 | -99 | -76 |
| 30 mg/kg | Example 111 | -100 | -65 |
| 30 mg/kg | Example 5 | -96 | -89 |
| 30 mg/kg | Example 6 | -84 | -49 |
| 30 mg/kg | Example 11 | -63 | -26 |
| 30 mg/kg | Example 8 | -38 | -34 |
| 100 mg/kg | Example 24 | -86 | -41 |
| 100 mg/kg | U-0521 | -34 | -14 |

The results indicate that the compounds according to the invention are even more than thousand times more potent in vitro (Table 1) than the reference compound (U-0521). The orally administered new compounds inhibit COMT also in vivo significantly better than the

reference compound, which is reflected as decreased serum 3-OMD concentration (Table 2). The reference compound U-0521 furthermore penetrates the blood-brain barrier and nonspecifically inhibits tyrosine hydroxylase which is essential for the biosynthesis of catecholamines.

FIG. 1 shows the 3-OMD serum concentrations for the new compound (e.g. according to example 5) and for the control compound which does not contain COMT inhibitor. The experimental design is the same as for the in vivo experiments above. FIG. 2 shows the levodopa serum concentrations after the same treatments. These figures show that the compounds according to the invention increase the bioavailability of levodopa and decrease the level of the harmful metabolite 3-OMD. The change observed in serum is reflected in the brain concentrations of 3-OMD and levodopa.

Specificity of COMT inhibition

The new compounds are specifically comt inhibitors and not inhibitors of other essential enzymes. This was

shown in in vitro experiments which were performed as described above.

| Compound | COMT | TH | IC ₅₀ (nM) | | | |
|-------------|------|--------|-----------------------|----------|----------|----------|
| | | | DBH | DDC | MAO-A | MAO-B |
| Example 87 | 3 | 38,000 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |
| Example 11 | 5 | 18,000 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |
| Example 8 | 6 | 21,000 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |
| Example 6 | 12 | 50,000 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |
| Example 110 | 12 | 14,000 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |
| Example 19 | 16 | 17,500 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |
| Example 5 | 20 | 21,000 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |
| Example 111 | 24 | 50,000 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |
| U-0521 | 6000 | 24,000 | > 50,000 | > 50,000 | > 50,000 | > 50,000 |

TH=Thyrosine hydroxylase, DBH=Dopamine- β -hydroxylase MAO-A and -B=Monoamine oxidase-A and -B.

The COMT inhibitors according to the invention are extremely specific. They inhibit COMT effectively at low concentrations, while inhibition of other enzymes involved in the metabolism of catecholamines requires a 1000-10000 times higher concentration. The difference between the inhibition of TH and COMT in the reference compound U-0521 is only 4-fold.

IC₅₀ is the concentration which inhibits 50% of the enzyme activity.

Toxicity

The new COMT inhibitors are non-toxic. For instance, the LD₅₀ of 3-(3,4-dihydroxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (Example 11) given as an oral suspension to rats, was over 2500 mg/kg.

EXAMPLE 1

3-Nitro-5-[2-(4-pyridyl)vinyl]catechol

A solution containing 2.0 g (0.011 mole) of 3,4-dihydroxy-5-nitrobenzaldehyde and 2.23 g (0.024 mole) of 4-picoline in 9.0 ml of acetic anhydride was refluxed for 1 h. About 15 ml of isopropanol was then added and the solution was cooled to 0° C. where upon the diacetyl-derivative of the desired product crystallized. After filtration the product was suspended in 100 ml of 0.5 N hydrochloric acid and refluxed for 1.5 h. After cooling the precipitate was filtered, washed with water and acetone and dried. Yield 1.89 g (67%), m.p. above 350° C.

EXAMPLE 2

3-Nitro-5-[2-(4-quinolyl)vinyl]catechol

The same procedure described in Example 1 was repeated using 2.0 g (0.011 mole) of 3,4-dihydroxy-5-nitrobenzaldehyde and 3.44 g (0.024 mole) of 4-quinoline. Yield 1.7 g (50%), m.p. 250° C. (decomp.).

EXAMPLE 3

4-Hydroxy-3-methoxy-5-nitrocinnamic acid

A solution of 1.0 g of 5-nitrovanillin and 4.0 g of malonic acid in 10 ml of pyridine was heated for 50 h at 80° C. The reaction mixture was diluted with water, acidified with hydrochloric acid, filtered, washed with water and dried. Yield 0.44 g (36%). The ¹H-NMR spectrum was in accordance with the structure alleged.

EXAMPLE 4

3,4-Dihydroxy-5, ω -dinitrostyrene

A solution containing 3.66 g (0.02 mole) of 3,4-dihydroxy-5-nitrobenzaldehyde, 3.66 g (0.06 mole) of nitromethane and 3.31 g of ammonium acetate in 10 ml of abs. ethanol was refluxed for 6 h. Water was added to the reaction mixture. The mixture was acidified with hydrochloric acid and extracted with methylene chloride. The methylene chloride extract was washed with water and the solvent was evaporated in vacuo. The residue was crystallized from isopropanol, yield 1.9 g (40%), m.p. 258°-260° C.

EXAMPLE 5

3,4-Dihydroxy-5-nitro- ω,ω -dicyanostyrene

The same procedure described in Example 4 was repeated using 3.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 3.0 g of malonodinitrile. The product was crystallized from methanol-water, yield 1.9 g (50%), m.p. 205°-209° C.

EXAMPLE 6

4-(3,4-Dihydroxy-5-nitrophenyl)-3-methylbut-3-en-2-one

A solution containing 0.5 g of 3,4-dihydroxy-5-nitrobenzaldehyde in 2.0 ml of butanone was saturated with gaseous hydrogen chloride. After standing over night ether was added to the solution and it was filtered. The product was crystallized from isopropanol, yield 0.2 g (30%), m.p. 139°-141° C.

EXAMPLE 7

3-(3,4-Dihydroxy-5-nitrobenzylidene)-2,4-pentanedione

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.00 g of 2,4-pentanedione in 10 ml of tetrahydrofuran was saturated with gaseous hydrogen chloride. After standing over night at 5° C. the product was filtered and washed with ether. Yield 1.2 g (50%), m.p. 175°-178° C.

EXAMPLE 8

3-(3,4-Dihydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 0.55 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.36 g of acetophenone in 10 ml of methanol was saturated with gaseous hydrogen chloride. After standing over night at 5° C. the product was filtered and washed with methanol. Yield 0.55 g (68%), m.p. 192°-195° C.

EXAMPLE 9

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-methoxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.8 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.5 g of 4'-methoxyacetophenone in 20 ml of tetrahydrofuran. Yield 1.88 g (60 m.p. 222°-228° C.

EXAMPLE 10

3-

(3,4-Dihydroxy-5-nitrophenyl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.8 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.8 g of 3',4'-dimethoxyacetophenone in 20 ml of methanol. Yield 1.7 g (50%), m.p. 206°-208° C.

EXAMPLE 11

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 0.55 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.63 g of 3',4',5'-trimethoxyacetophenone. Yield 0.50 g (44%), m.p. 213°-216° C.

EXAMPLE 12

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(2-hydroxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.74 g of 2'-hydroxyacetophenone. Yield 0.2 g (12%), m.p. 231°-234° C.

EXAMPLE 13

3-(3,4-Diacetoxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 1.0 g of the product obtained in Example 8 in 5.0 ml of acetic anhydride was refluxed for 2 h. After cooling the product was filtered and washed with ether. Yield 0.73 g (68%), m.p. 183°-185° C.

EXAMPLE 14

3-(3,4-Dibenzoyloxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

1.0 g of the product obtained in Example 8 and 2.0 ml of benzoylchloride were dissolved in 5 ml of tetrahydrofuran. Tetrahydrofuran was distilled off to a great extent and the residue was refluxed for 2 h. After cooling ether was added to the mixture and the product was filtered and triturated with ethylmethylketone. Yield 0.50 g (29%), m.p. 206°-210° C.

EXAMPLE 15

3-(3-Pivaloyloxy-4-hydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

1.0 g of the product obtained in Example 8 was dissolved in 5 ml of tetrahydrofuran, 4.7 ml of pivaloyl chloride was added and the mixture was refluxed for 16 h. The solvent was evaporated in vacuo and the residue was purified in a silicagel column by using toluene-acetic acid-dioxane (18:1:1) mixture as an eluent. The product was crystallized from ether, m.p. 148°-150° C.

EXAMPLE 16

4-(3,4-Dihydroxy-5-nitrophenyl)-3-methylbut-3-en-2-ol

1.8 g of the product obtained in Example 6 was dissolved in 20 ml of 1N NaOH-solution and 4.0 g of sodium borohydride in small amount of water was added. The mixture was stirred over night at room temperature, acidified with hydrochloric acid and extracted with ether. The solvent was evaporated in vacuo and the residue purified in a silica gel column by using toluene-acetic acid dioxane (18:1:1). The product was crystallized from dichloromethane petroleum ether. Yield 0.80 g (44%), m.p. 102°-104° C.

EXAMPLE 17

7-(3,4-Dihydroxy-5-nitrobenzylidene)-8-ketononanoic acid

The procedure described in Example 9 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.72 g of 8-ketononanoic acid. Yield 1.85 g (55%), yellow viscous oil.

EXAMPLE 18

4'-Hydroxy-3'-methoxy-5'-nitroacetophenone

To a solution containing 40 ml of nitric acid (d-1.41) and 40 ml of water was gradually added while cooling (below 7° C.) and stirring 25.0 g of 4'-hydroxy-3'-methoxyacetophenone. After stirring for 0.5 h at 0° C. the product was filtered, washed first with diluted nitric acid (1:1) and then with water. Yield 24.0 g (75%). The ¹H-NMR-spectrum of the product was in accordance with the structure alleged.

EXAMPLE 19

3,4-Dihydroxy-5'-nitroacetophenone

A solution containing 19.9 g of the product obtained in Example 18 in 200 ml of acetic acid and 200 ml of 48% hydrobromic acid was refluxed for 5 h. 500 ml of a saturated solution of sodium sulfate was added to the reaction mixture and the same was let stand overnight at 5° C. The solution was extracted with ether. The ether phase was washed with 200 ml of water, dried and the solvent evaporated in vacuo. The residue was crystallized from isopropanol. Yield 10.2 g (35 m.p. 155°-159° C.

EXAMPLE 20

1-(3,4-Dihydroxy-5-nitrophenyl)-3-(4-dimethylamino-phenyl)-prop-2-en-1-one

A solution containing 0.5 g of the product obtained in Example 19 and 0.38 g of 4-dimethylaminobenzaldehyde in 5 ml of methanol was saturated with gaseous hydrogen chloride. The solution was refluxed for 1 h. After cooling the product was filtered and washed with methanol. Yield 0.26 g (70%), decomp. on heating.

EXAMPLE 21

5-(4-Benzoyloxy-3-methoxyphenyl)-2,4-pentadienoic acid

To a solution containing 260 g of 4-benzoyloxy-3-methoxybenzaldehyde and 200 ml of ethyl crotonate in 1200 ml of N-methylpyrrolidone was gradually added while stirring and cooling at 0° C. 149.6 g of potassium tert.-butoxide. The solution was stirred for 0.5 h after which 200ml of 10 N NaOH-solution was added and

stirred for 0.5 h more at 0° C. The reaction mixture was added to a mixture of hydrochloric acid and ice. The semisolid product was separated and used without purification to the next step.

EXAMPLE 22

(4-Hydroxy-3-methoxyphenyl)pentanoic acid

The raw product obtained in Example 21 was dissolved in 500 ml of N,N-dimethylformamide and 22 g of 10% palladium on charcoal catalyst was added. The mixture was hydrogenated at 60° C. and normal pressure until the theoretical amount (3 mole) of hydrogen was consumed. After filtering the solvent was evaporated in vacuo to a great extent and the residue was dissolved in 1 l of dichloromethane and washed with 2 l of water. The product was extracted with 1.5 l of saturated NaHCO₃-solution. After acidification of the aqueous phase with hydrochloric acid the product was extracted with 1 l of dichloromethane. The solvent was distilled off in vacuo and the semisolid residue (180 g) was used to the next step.

EXAMPLE 23

5-(4-Hydroxy-3-methoxy-5-nitrophenyl)pentanoic acid

The above product (180 g) was dissolved in 1 l of dichloromethane and 820 ml of 1 molar HNO₃-dichloromethane solution was added gradually while stirring and cooling (0°-5° C.). The solution was stirred for 10 min more at 0° C. after which water was added. The organic phase was separated and washed with water. The solvent was evaporated in vacuo and the semisolid residue was used as such to the next step.

EXAMPLE 24

5-(3,4-Dihydroxy-5-nitrophenyl)pentanoic acid

The above product obtained in Example 23 was dissolved in a mixture containing 500 ml of acetic acid and 500 ml of 48% hydrobromic acid and refluxed for 4 h. 1 l of saturated Na₂SO₄-solution was added to the reaction mixture and the solution was allowed to stand over night at 5° C. The product crystallized was filtered and washed with 50% acetic acid. This product was recrystallized from ethyl acetate. Yield 32 g (16%), m.p. 135°-138° C.

EXAMPLE 25

1-Benzyl-4-[5-(3,4-dihydroxy-5-nitrophenyl)pentanoyl]piperazine hydrochloride

A solution containing 3.0 g of the product obtained in Example 24 in 18 ml of thionyl chloride was refluxed for 10 min. The excess of thionyl chloride was evaporated in vacuo and the acid chloride formed was dissolved in 20 ml of dichloromethane. To this solution 2.1 g of 1-benzylpiperazine in 20 ml of dichloromethane was added with stirring and stirred for 0.5 h more. Ether was added to the reaction mixture and the crystals were filtered. Yield 3.55 g (73%), m.p. 85°-89° C.

EXAMPLE 26

N-Isopropyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

A solution containing 0.5 g of the product obtained in Example 24 in 2.5 ml of thionyl chloride was refluxed for 10 min. The excess of thionyl chloride was evaporated in vacuo and the residue dissolved in 25 ml of dichloromethane. To this solution 0.47 g of isopropylamine was added and the mixture was stirred for 1 h at 20° C. Dichloromethane phase was washed with 1 N hydrochloric acid and evaporated in vacuo. The residue was crystallized from toluene. Yield 0.44 g (75%), m.p. 113°-115° C.

EXAMPLE 27

N-Methyl

(N-propargyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

The procedure described in Example 26 was repeated using 0.5 g of methyl-propargylamine instead of isopropylamine. Yield 0.5 g (83%), mp. 133°-135° C.

EXAMPLE 28

N-(1-Adamantyl)-5-(3,4-dihydroxy-5-nitrophenyl)pentanoic amide

The procedure described in Example 26 was repeated using 1.5 g of 1-aminoadamantane instead of isopropylamine. Yield 0.61 g (80%), m.p. 157°-160° C.

EXAMPLE 29

Tetradecyl-5-(3,4-dihydroxy-5-nitrophenyl)pentanoate

The procedure described in Example 26 was repeated using 1.26 g of 1-tetradecanol instead of isopropylamine. The reaction mixture was washed with water and the solvent evaporated in vacuo. Yield 0.44 g (50%), m.p. 46°-47° C.

EXAMPLE 30

Tetradecyl-5-(3,4-diacetoxy-5-nitrophenyl)pentanoate

A solution containing 0.1 g of the product obtained in Example 29 in 2 ml of acetic anhydride was refluxed for 20 min. The solvent was evaporated in vacuo and the residue crystallized from petroleum ether (b.p. 40° C.). m.p. 52°-54° C.

EXAMPLE 31

Tetradecyl-5-(4-hydroxy-3-pivaloyloxy-5-nitrophenyl)pentanoate

The procedure described in Example 30 was repeated using 2 ml of pivaloyl chloride instead of acetic anhydride. The product was a viscous oil.

EXAMPLE 32

5-(3,4-Dimethoxy-5-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 10.0 g of 3,4-dimethoxy-5-chlorobenzaldehyde and 8.3 ml of ethyl crotonate in 65 ml of N-methylpyrrolidone 6.7 g of potassium tert-butoxide was added with stirring. The solution was stirred for 0.5 h more at 20° C. and the solution was poured then to a mixture of ice and hydrochloric acid and extracted with ether. The ether extract was washed with water and extracted then with NaHCO₃-solution. The aqueous phase was acidified with hydrochloric acid and the semisolid product was separated and washed with water. Yield 7.3 g (55%).

EXAMPLE 33

5-(3,4-Dimethoxy-5-chlorophenyl)pentanoic acid

A solution containing 6.2 g of the above product obtained in Example 32 was dissolved in a mixture of 30 ml of acetic acid and 3 ml of conc. hydrochloric acid. Palladium on charcoal catalyst (10% Pd) was added

and the mixture was hydrogenated at normal pressure and room temperature. After filtration the solvents were evaporated in vacuo. Yield 3.2 g (55%), a viscous oil.

EXAMPLE 34

5-(3,4-Dihydroxy-5-chlorophenyl)pentanoic acid

A solution containing 3.2 g of the above product in 8 ml of acetic acid and 10 ml of 48% hydrobromic acid was refluxed for 3 h. A saturated solution of Na_2SO_4 in water was added to the reaction mixture. The crystallized product was filtered, washed with water and recrystallized from toluene, m.p. $99^\circ\text{--}101^\circ\text{C}$.

EXAMPLE 35

5-(3,4-Dimethoxy-6-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 10.0 g 3,4 dimethoxy-6-chlorobenzaldehyde and 8 ml of ethyl crotonate in 60 ml of N-methylpyrrolidone 6.0 g of potassium tert-butoxide was added while stirring. The solution was stirred for 0.5 h more at 20°C . and poured then to a mixture of ice and hydrochloric acid. The solution was extracted with ether. The ether solution was washed with water and extracted with 2.5 N NaOH-solution. The aqueous phase was acidified with hydrochloric acid and the semisolid product was separated. Yield 10.8 g (81%).

EXAMPLE 36

5-(3,4-Dihydroxy-6-chlorophenyl)-2,4-pentadienoic acid

To a solution containing 0.54 g of the product obtained in Example 35 in 6 ml dichloromethane 6 ml of 1 molar boron tribromide-dichloromethane solution was added and stirred for 24 h at 20°C . The solvent was evaporated in vacuo and 2 N hydrochloric acid was added to the residue. The product was filtered and washed with water. Recrystallization from isopropanol-water yielded 0.22 g (46%) of the product desired, m.p. $203\text{--}206^\circ\text{C}$.

EXAMPLE 37

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-methylphenyl)-prop-2-en-1-one

A solution containing 5.49 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 5.37 g of 4'-methylacetophenone in 50 ml of tetrahydrofuran was added a catalytic amount of gaseous hydrogen chloride and refluxed for 4.5 h. The solvent was evaporated in vacuo and the residue crystallized from ether-petroleum-ether, yield 1.85 g (21%), m.p. $184^\circ\text{--}186^\circ\text{C}$.

EXAMPLE 38

5-(3,4-Dimethoxyphenyl)-5-ketopentanoic acid

A solution containing 36 g of veratrole and 30 g glutaric anhydride in 120 ml of nitrobenzene was gradually added while stirring and cooling at 0°C . to a mixture of 72 g of anhydrous aluminium chloride and 240 ml of nitrobenzene. The mixture was stirred for 1 h at 0°C . and then for 18 h at 20°C . Ice and hydrochloric acid were added to the reaction mixture. Nitrobenzene layer was separated and to this ethyl acetate was added whereupon the product crystallized. After filtering the crystals were washed with ethyl acetate. Yield 42.3 g (64%).

EXAMPLE 39

5-(3,4-Dimethoxyphenyl)pentanoic acid

A mixture containing 37.6 g of the product obtained in Example 38 and 64 g of zinc turnings (treated with a solution of HgCl_2), 55 ml of toluene and 220 ml of conc. hydrochloric acid was refluxed for 1 h. Toluene phase was separated and evaporated in vacuo. The residue was crystallized from toluene-petroleum ether, yield 11.5 g (32%).

EXAMPLE 40

5-(3,4-Dimethoxy-6-nitrophenyl)pentanoic acid

15.0 g of product described in Example 39 was gradually added to 75 ml of nitric acid (d-1.41) at 20°C . The mixture was stirred for 20 min more. Ice-water was added and solution was extracted with dichloromethane. The solvent was evaporated in vacuo yielding 14.0 g (79%) of the desired product.

EXAMPLE 41

5-(3,4-Dihydroxy-6-nitrophenyl)pentanoic acid

A solution containing 42.0 g of the product obtained in Example 40 in 100 ml of acetic acid and 150 ml of 48% hydrobromic acid was refluxed for 10 h. 1 l of saturated Na_2SO_4 -solution was added to the reaction mixture and extracted with ether. The solvent was evaporated in vacuo and the residue crystallized from ethyl acetate-petroleum ether. Yield 7.9 g (19%), m.p. $111^\circ\text{--}114^\circ\text{C}$.

EXAMPLE 42

3-(3,4-Dimethoxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

A solution containing 2.0 g of product described in Example 2 and 5 ml of mesyl chloride in 20 ml of N-methylpyrrolidone was heated for 1.5 h at 100°C . After cooling, water was added and the solution was extracted with ether. The solvent was evaporated in vacuo and the residue was crystallized from 1-propanol. Yield 0.14 g, m.p. $181^\circ\text{--}184^\circ\text{C}$.

EXAMPLE 43

N-(1-Adamantyl)-3,4-diacetoxy-5-nitrobenzamide

A solution containing 0.85 g of 3,4-diacetoxy-5-nitrobenzoic acid and 0.32 ml of thionyl chloride and a catalytic amount of N,N-dimethylformamide in 10 ml of toluene was heated for 1 h at 80°C . The solvent was evaporated in vacuo and the residue was dissolved in 5 ml of dichloromethane and added to a mixture containing 0.56 g of 1-aminoadamantane hydrochloride and 0.94 ml of triethylamine in 10 ml of dichloromethane and stirred for 15 min at 0°C . and then 15 min at 20°C . Water was added to the reaction mixture and dichloromethane phase was separated. The solvent was evaporated in vacuo yielding yellow viscous oil 1.2 g (100%).

EXAMPLE 44

N-(1-Adamantyl)-3,4-dihydroxy-5-nitrobenzamide

A solution containing 1.2 g of the product obtained in Example 43 and a catalytic amount of sulfuric acid in 10 ml of methanol was refluxed for 3 h. 20 ml of water was added and on cooling 0.85 g (89.5%) of the desired product was crystallized, m.p. $207^\circ\text{--}208^\circ\text{C}$.

EXAMPLE 45

4-Cyclohexylcarbonyl-1-(3,4-diacetoxy-5-nitrobenzoyl)piperidine

The procedure described in Example 43 was repeated using 0.58 g of cyclohexylcarbonylpiperidine and 0.38 ml 2,6-lutidine instead of 1-aminoadamantane hydrochloride and triethylamine respectively. Yield 1.2 g (87%), a viscous yellow oil.

EXAMPLE 46

4-Cyclohexylcarbonyl-1-(3,4-dihydroxy-5-nitrobenzoyl)piperidine

The procedure described in Example 44 was repeated using 1.2 g of the product obtained in Example 45. Yield 0.5 g (50%), m.p. 155°-165° C.

EXAMPLE 47

N-Benzyl-3,4-diacetoxy-5-nitrobenzamide

0.75 g of 3,4-diacetoxy-5-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was dissolved in 5 ml of dichloromethane and added to a solution containing 0.27 ml of benzylamine and 0.5 ml of 2,6-lutidine in 7 ml of dichloromethane. Yield 0.95 g (96%), a viscous oil.

EXAMPLE 48

N-Benzyl-3,4-dihydroxy-5-nitrobenzamide

The procedure described in Example 44 was repeated using 0.95 g of the product obtained in Example 47. Yield 0.5 g (68%), m.p. 185°-189° C.

EXAMPLE 49

N-(1-Adamantyl)-3,4-cyclohexyldenedioxy-6-nitrobenzamide

2 g of 3,4-cyclohexyldenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 1.1 g of 1-aminoadamantane and 1.1 ml of triethylamine in 15 ml of dichloromethane. Yield 2.9 g (98%), a viscous oil.

EXAMPLE 50

N-(1-Adamantyl)-3,4-dihydroxy-6-nitrobenzamide

A solution containing 0.5 g of the product obtained in Example 49 and 0.09 ml of methanesulfonic acid in 8 ml of 98% formic acid was heated for 15 min at 60° C. The solvent was evaporated in vacuo and water was added to the residue. Yield 0.35 g (88%), m.p. 250°-255° C.

EXAMPLE 51

N-(4-Morpholinoethyl)-3,4-cyclohexyldenedioxy-6-nitrobenzamide

2.0 g of 3,4-cyclohexyldenedioxy-6-nitrobenzoic acid was converted into the corresponding acid chloride like described in Example 43. It was added to a solution containing 0.9 ml of 4-(2-aminoethyl)morpholine and 1.1 ml of triethylamine in 15 ml of dichloromethane. Yield 2.5 g (89%), a viscous oil.

EXAMPLE 52

N-(4-Morpholine ethyl)-3,4-dihydroxy-6-nitrobenzamide hydromesylate

The procedure described in Example 50 was repeated using 1.95 g of the product obtained in Example 51.

Yield 0.8 g (40%), viscous oil. The ¹H-NMR-spectrum was in accordance with the alleged structure.

EXAMPLE 53

N-(1-Adamantyl)-3,4-diacetoxy-5-chlorobenzamide

0.7 g of 3,4-diacetoxy-5-chlorobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 1.0 g (95%), a viscous oil.

EXAMPLE 54

N-(1-Adamantyl)-3,4-dihydroxy-5-chlorobenzamide

The product of Example 53 was deacetylated like described in Example 44. Yield 0.6 g (78%), m.p. 244°-247° C.

EXAMPLE 55

N-(1-Adamantyl)-3,4-cyclohexyldenedioxy-6-chlorobenzamide

0.8 g of 3,4-cyclohexyldenedioxy-6-chlorobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 1.0 g (83%), viscous oil.

EXAMPLE 56

N-(1-Adamantyl)-3,4-dihydroxy-6-chlorobenzamide

1.0 g of the product obtained in Example 55 was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.65 g (81%), m.p. 225°-230° C.

EXAMPLE 57

N-(1-Adamantyl)-3,4-diacetoxy-5-cyanobenzamide

0.6 g of 3,4-diacetoxy-5-cyanobenzoic acid was converted to the corresponding acid chloride and the procedure described in Example 43 was repeated. Yield 0.75 g (88%), viscous oil.

EXAMPLE 58

N-(1-Adamantyl)-3,4-dihydroxy-5-cyanobenzamide

0.75 g of the above product was deacetylated as described in Example 44. Yield 0.5 g (89%), m.p. 253°-255° C.

EXAMPLE 59

1-Butyl-3,4-dihydroxy-5-cyanobenzoate

A solution containing 0.5 g of 3,4-dihydroxy-5-cyanobenzoic acid in 10 ml of 1-butanol was saturated with gaseous hydrogen chloride at 0° C. The solution was then heated for 3 h at 100° C. The solvent was evaporated in vacuo and dichloromethane was added to the residue. The formed crystals were filtered. Yield 0.19 g (30%), m.p. 135°-140° C.

EXAMPLE 60

ω -(2-Methylpiperidyl)-3,4-dimethoxy-6-cyanopropionanilide

A mixture containing 2.68 g of ω -chloro-3,4-dimethoxy-6-cyanopropionanilide, 1.5 g of 2-methylpiperidine, 1.4 g of CaO and a catalytic amount of potassium iodide in 15 ml of toluene was heated for 18 h at 100° C. The solution was filtered, washed with water and evaporated in vacuo. The residue was treated with petro-

leum ether and filtered. Yield 2.79 g (84%), m.p. 126°-127° C.

EXAMPLE 61

ω -(1-Adamantylamino)-3,4-dimethoxy-6-cyanopropionanilide

A mixture containing 3.0 g of ω -chloro-3,4-dimethoxy-6-cyanopropionanilide, 2.3 g of 1-aminoadamantane hydrochloride, 4.6 g of potassium carbonate and a catalytic amount of potassium iodide in 15 ml of toluene was heated while stirring for 6 h at 100° C. The solution was filtered and the solvent evaporated in vacuo. Water was added to the residue and the product was filtered. Yield 3.4 g (74%), m.p. 137°-140° C.

EXAMPLE 62

1-(3,4-Cyclohexylidenedioxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

0.5 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 0.35 g of 4-cyclohexylcarbonylpiperidine and 0.2 g of triethylamine in 30 ml of dichloromethane. Yield 0.7 g (85%), m.p. 270° C.

EXAMPLE 63

1-(3,4-Dihydroxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

0.48 g of the above product was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.3 g (75%), m.p. 240° C.

EXAMPLE 64

1-(3,4-Cyclohexylidenedioxy-6-nitrobenzoyl)-4-(1-piperidyl)piperidine

The procedure described in Example 62 was repeated using 0.3 g of 4-(1-piperidyl)piperidine instead of 4-cyclohexylcarbonylpiperidine. Yield 0.57 g (74%), m.p. 200° C.

EXAMPLE 65

Cyclohexyl-4-[1-(3,4-cyclohexylidenedioxy-6-nitrobenzoyl)piperidyl]carbinol

To a solution containing 0.5 g of the product obtained in Example 62 and 1.1 ml of 1N NaOH in 20 ml of methanol 0.1 g of sodium borohydride was added at room temperature. The solution was acidified with acetic acid and extracted with dichloromethane. The solvent was removed in reduced pressure and the residue treated with petroleum ether. Yield 0.45 g (90%), m.p. 155° C.

EXAMPLE 66

1-(3,4-Dihydroxy-6-nitrobenzoyl)-4-(1-piperidyl)piperidine hydromesylate

0.3 g of the product obtained in Example 64 was treated with methanesulfonic acid in formic acid as described in Example 50. Yield 0.26 g (84%), m.p. 290° C.

EXAMPLE 67

1-(3,4-Diacetoxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

0.5 g of the product obtained in Example 63 was heated in 10 ml of acetic anhydride for 1 h at 40° C.

Ice-water was added and the product was filtered. Yield 0.5 g (87%), m.p. 160°-165° C.

EXAMPLE 68

5 N-Methyl-N-propargyl-3,4-cyclohexylidenedioxy-6-nitrobenzamide

0.5 g of 3,4-cyclohexylidenedioxy-6-nitrobenzoic acid was converted to the corresponding acid chloride and added to a solution containing 0.12 g methylpropargylamine and 0.18 g of triethylamine in 20 ml of dichloromethane. Yield 0.3 g (50%), m.p. 50°-55° C.

EXAMPLE 69

15 1-(3,4-Dimethoxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

10.3 g of 3,4-dimethoxy-6-nitrobenzoic acid was converted to the corresponding acid chloride as described in Example 43. It was added to a solution containing 8.83 g of 4-cyclohexylcarbonylpiperidine and 4.58 g of triethylamine in 300 ml of dichloromethane. Yield 16.4 g (90%), m.p. 120°-125° C.

EXAMPLE 70

25 1-(3,4-Dihydroxy-6-nitrobenzoyl)-4-cyclohexylcarbonylpiperidine

A solution containing 0.81 g of the above compound in 12 ml of 1 molar $\text{BBr}_3\text{-CH}_2\text{Cl}_2$ was stirred over night at 20° C. Water was added and the product was filtered. Yield 0.5 g (67%), m.p. 240° C.

EXAMPLE 71

Cyclohexyl-4-[1-(3,4-dimethoxy-6-nitrobenzoyl)piperidyl]carbinol

35 2.03 g of the product obtained in Example 69 was reduced with sodium borohydride as described in Example 65. Yield 1.89 g (93%), m.p. 145°-150° C.

EXAMPLE 72

3-(3-Ethoxycarbonylmethylcarbamoxyloxy-4-hydroxy-5-nitrophenyl)-1-phenylprop-2-en-1-one

45 1.5 g of ethyl isocyanatoacetate was added to a solution containing 0.54 g of the product obtained in Example 8 in 10 ml of tetrahydrofuran and the solution was stirred for 3 days at 20° C. The solvent was evaporated in reduced pressure and the raw product was purified in a silica gel column using toluene-dioxane-acetic acid (8:1:1) as an eluent. Crystallization from acetone-petroleum ether yielded 0.13 g (17%) of the desired product desired, m.p. 155°-158° C.

EXAMPLE 73

55 3-(3,4-Methylenedioxy-6-nitrophenyl)-1-phenylprop-2-en-1-one

The procedure described in Example 8 was repeated by using 1.95 g of 6-nitropiperonal and 2.10 g of 3',4',5'-trimethoxyacetophenone in 30 ml of methanol. Yield 0.88 (24%), m.p. 157°-159° C.

EXAMPLE 74

3-(4-Hydroxy-3-methoxy-5-nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

65 The procedure described in Example 8 was repeated by using 2.0 g of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde and 2.1 g of 3',4',5'-trimethoxyacetophenone. Yield 2.2 g (57%), m.p. 123°-125° C.

EXAMPLE 75

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(2-carboxyphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.64 g of 2'-carboxyacetophenone. Yield 0.36 g (11%), m.p. 178-180° C.

EXAMPLE 76

3-(3,4-Dihydroxy-5-nitrophenyl)-1-(4-nitrophenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.65 g of 4'-nitroacetophenone. Yield 1.25 g (38%), m.p. 255°-256° C.

EXAMPLE 77

3-(3-methoxy-4-hydroxy-5-trifluoromethylphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

The procedure described in Example 8 was repeated using 2.2 g of 3-methoxy-4-hydroxy-5-trifluoromethylbenzaldehyde and 2.1 g of 3',4',5'-trimethoxyacetophenone. Yield 2.6 g (61%), m.p. 190°-192° C.

EXAMPLE 78

4-(3,4-Dimethoxy-5-methylsulfonylphenyl)-3-methylbut-3-en-2-one

The procedure described in Example 8 was repeated using 2.44 g of 3,4-dimethoxy-5-methylsulfonylbenzaldehyde and 1.0 g of 2-butanone. Yield 2.0 g (63%), viscous oil.

EXAMPLE 79

2,5-Bis-(3,4-dihydroxy-5-nitrobenzylidene)cyclopentanone

The procedure described in Example 8 was repeated using 5.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 2.0 g of cyclopentanone. Yield 4.4 g (78%), m.p. 300° C. (decomp.).

EXAMPLE 80

1-Phenyl-3-(3-stearoyloxy-4-hydroxy-5-nitrophenyl)-prop-2-en-1-one

A solution containing 2.0 g of the product obtained in Example 8 and 10.0 g of stearoyl chloride in 10 ml of dioxane was stirred and heated for 18 h at 90° C. After cooling petroleum ether was added and the product was filtered. Recrystallization from dichloromethane-petroleum ether yielded 0.64 g (17%) of the desired product desired, m.p. 112°-118° C.

EXAMPLE 81

Ethyl 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate

The procedure described in Example 4 was repeated using 1.0 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 0.9 g of ethyl cyanoacetate and 0.15 g of ammonium acetate in 10 ml of ethanol. Yield 0.87 g (57%), m.p. 205°-210° C.

EXAMPLE 82

Methyl

3-(3,4-dihydroxy-5-nitrobenzylidene)-4-ketopentanoate

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.1 g of levulinic acid in 10 ml of

methanol was saturated with gaseous hydrogen chloride. The mixture was refluxed for 20 h after which water was added and the solution was extracted with ether. The solvent was evaporated in reduced pressure and the residue crystallized from ether-petroleum ether. Yield 0.54 g (20%), m.p. 142°-150° C.

EXAMPLE 83

3,4-Dihydroxy-5-nitrobenzylmalonitrile

1.5 g of sodium borohydride was added to a suspension containing 3.7 g of the product obtained in Example 5 in 10 ml of water at room temperature. The solution was stirred for 2 h more, acidified with hydrochloric acid and extracted with ether. The solvent was evaporated in vacuo and the residue crystallized from methanol-isopropanol. Yield 1.1 g (30%), m.p. 211°-215° C.

EXAMPLE 84

Ethyl 3,4-dihydroxy-5-nitrobenzylcyanoacetate

The procedure described in Example 83 was repeated using 2.78 g of the product obtained in Example 81. Yield 0.98 g (35%), yellow viscous oil.

EXAMPLE 85

1-Phenyl-3-(3-methoxy-4-hydroxy-5-trifluoromethylphenyl)-prop-2-en-1-one

The procedure described in Example 8 was repeated using 1.7 g of 3-methoxy-4-hydroxy-5-trifluoromethylbenzaldehyde and 1.0 g of acetophenone. Yield 1.1 g (45%), m.p. 166°-168° C.

EXAMPLE 86

1-Phenyl-3-(3,4-dihydroxy-5-trifluoromethylphenyl)-prop-2-en-1-one

To a solution containing 0.32 g of the above product obtained in Example 85 in 10 ml of dichloromethane 3 ml of 1 molar BBr₃-CH₂Cl₂ was added. The mixture was stirred for 20 min at room temperature, acidified with 10 ml 2 N hydrochloric acid and extracted with dichloromethane. The solvent was evaporated in reduced pressure and the residue crystallized from acetone-dichloromethane. Yield 0.07 g (23%), m.p. 196°-201° C.

EXAMPLE 87

3,4-Dihydroxy-5-sulfonamidobenzaldehyde

A solution containing 1.89 g of 2,3-dihydroxybenzenesulfonamide and 1.4 g of hexamethylenetetramine in 20 ml of trifluoroacetic acid was refluxed for 2 h. The solvent was evaporated in vacuo, water was added to the residue and the product was filtered. Yield 0.78 g (35%).

EXAMPLE 88

2-Methoxy-6-trifluoromethylphenol

A solution containing 160 ml of 1.6 molar butyllithium in hexane, 300 ml of tetrahydrofuran and 40 ml of N,N,N',N'-tetramethylethylenediamine was cooled to -78° C. and 43.3 g of 3-trifluoromethylanisole was added with stirring under nitrogen atmosphere. The solution was allowed to warm up to room temperature and cooled then again to -78° C. after which 35 ml of trimethyl borate was added. The solution was warmed up to 20° C. and 50 ml of conc. ammonia solution was

added. The solvents were evaporated in reduced pressure and to the residue 60 ml of 98–100% formic acid followed with 25 ml of 35% hydrogen peroxide were added. The solution was extracted with ether-petroleum ether (1:1). The organic phase was separated and the product was extracted with 2.5 N NaOH-solution. The aqueous phase was acidified with hydrochloric acid and the product was extracted in dichloromethane. The solvent was removed for the most part in vacuo after which petroleum ether was added. The crystalline product was filtered, yield 8.5 g (18%), m.p. 51°–53° C.

EXAMPLE 89

4-Hydroxy-3-methoxy-5-trifluoromethylbenzaldehyde

A solution containing 1.9 g of 2-methoxy-6-trifluoromethylphenol and 1.4 g of hexamethylenetetramine in 20 ml of trifluoroacetic acid was refluxed for 1 h. The solvent was removed in reduced pressure, 50 ml of 1 N hydrochloric acid was added to the residue and the solution was extracted with dichloromethane. Most part of the solvent was evaporated in vacuo and petroleum ether was added, whereupon the product crystallized. Yield 0.7 g (32%), m.p. 151°–152° C.

EXAMPLE 90

3,4-Dimethoxy-5-cyanobenzaldehyde

A mixture containing 2.5 g of 3,4-dimethoxy-5-bromobenzaldehyde and 1.0 g of cuprous cyanide in N-methylpyrrolidone was refluxed for 2 h. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated in vacuo. Yield 1.55 g (81%), m.p. 109°–112° C.

EXAMPLE 91

3,4-Dihydroxy-5-cyanobenzaldehyde

A solution containing 0.96 g of the above product in 15 ml of 1 molar $\text{BBr}_3\text{--CH}_2\text{Cl}_2$ -solution was stirred for 4 h at room temperature under nitrogen. 15 ml of 1 N hydrochloric acid was added and the dichloromethane phase was separated. The solvent was evaporated in vacuo. Yield 0.61 g (75%), m.p. 210°–215° C.

EXAMPLE 92

1,2-Dimethoxy-3-methylsulfonylbenzene

To a solution containing 3.68 g of 2,3-dimethoxythianisole in 50 ml of dichloromethane 3.6 g of 3-chloroperoxybenzoic acid was added with stirring. Stirring was continued for 18 h more at room temperature. 30 ml of 1 N NaOH-solution was added, dichloromethane phase was separated and the solvent evaporated in vacuo. Yield 4.51 g (91%), a viscous oil.

EXAMPLE 93

3,4-Dimethoxy-5-methylsulfonylbenzaldehyde

The procedure described in Example 89 was repeated using 2.16 g of 2 hexamethylenetetramine. Yield 0.97 g (45%), a viscous oil.

EXAMPLE 94

3,4-Dihydroxy-5-methylsulfonylbenzaldehyde

A solution containing 0.5 g of the above product and 5 ml of 48% hydrobromic acid in 5 ml of acetic acid was refluxed for 8 h. Water was added and the solution was

extracted with dichloromethane. The solvent was evaporated in vacuo. Yield 0.3 g (68%), a viscous oil.

EXAMPLE 95

3,4-Dihydroxy-5-cyanobenzaldehyde

A solution containing 1.35 g of 2,3-dihydroxybenzonitrile and 1.4 g of hexamethylene tetramine in 20 ml of trifluoroacetic acid was refluxed for 1.5 h. Water was added and the product was filtered. Yield 0.9 g (55%), m.p. 211°–215° C.

EXAMPLE 96

3-(3,4-Dihydroxy-5-trifluoromethylphenyl)-1-phenylprop-2-en-1-one

The procedure described in Example 8 was repeated using 2.06 g of 3,4-dihydroxy-5-trifluoromethylbenzaldehyde and 1.20 g of acetophenone. Yield 2.19 g (71%), m.p. 196°–210° C.

EXAMPLE 97

3,4-Dihydroxy-5-trifluoromethylbenzaldehyde

A solution containing 2.2 g of 4-hydroxy-3-methoxy-5-trifluoromethylbenzaldehyde in 65 ml of 1 molar BBr_3 in dichloromethane was stirred for 2 h at room temperature. Hydrochloric acid was added and the organic phase was separated. The solvent was evaporated in vacuo. Yield 1.4 g (68%), m.p. 188°–192° C.

EXAMPLE 98

2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

A solution containing 1.3 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 0.73 g of cyanoacetamide and catalytic amount of piperidine acetate in 40 ml of dry ethanol was refluxed over night. The solvent was evaporated in vacuo and the residue was recrystallized water-DMF. Yield 0.84 g (48%), m.p. 296°–298° C.

EXAMPLE 99

N,N-Dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

A solution containing 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde, 1.2 g of N,N-dimethylcyanoacetamide and catalytic amount of piperidine acetate in 40 ml of dry ethanol was refluxed over night. Yield 1.1 g (40%), m.p. 183°–185° C.

EXAMPLE 100

N,N-Diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.5 g of N,N-diethylcyanoacetamide. Yield 2.23 g (73%), m.p. 153°–156° C.

EXAMPLE 101

N-Isopropyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.3 g of N-isopropylcyanoacetamide. Yield 1.46 g (50%), m.p. 243°–245° C.

EXAMPLE 102

N'-Methyl-N''-[2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acryl]piperazine

The procedure described in Example 99 was repeated using 1.83 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 1.7 g of N'-methyl-N''-cyanoacetyl piperazine. Yield 2.16 g (65%), m.p. 65° C. (decomp.).

EXAMPLE 103

3-(3,4-Dihydroxy-5-trifluoromethylbenzylidene)-2,4-pentanedione

The procedure described in Example 7 was repeated using 2.06 g of 3,4-dihydroxy-5-trifluoromethylbenzaldehyde and 1.00 g of 2,4-pentanedione. Yield 1.39 g (45%), m.p. 98°-205° C.

EXAMPLE 104

3,4-Dihydroxy-5-nitrobenzylalcohol

To a solution containing 6.0 g of sodium borohydride in 50 ml of water 9.15 g of 3,4-dihydroxy-5-nitrobenzaldehyde was gradually added with stirring at room temperature. The mixture was stirred for 1 h more after which it was acidified with hydrochloric acid. The solution was filtered to remove tarry impurities and extracted 4 times with ether. The ether extract was dried over anhydrous sodium sulfate, filtered and concentrated to a volume of about 100 ml.

The crystalline solid was filtered. Yield 6.0 g (65%), m.p. 100° C. (decomp.).

EXAMPLE 105

3,4-Dihydroxy-5-nitrobenzyl-2-methoxyethyl ether

A solution of 1.0 g of 3,4-dihydroxy-5-nitrobenzylalcohol in 5.0 ml of 2-methoxyethanol was refluxed for 1 h. The solvent was evaporated in vacuo and the residue was triturated with isopropanol. Yield 0.4 g (30%), m.p. 154°-157° C.

EXAMPLE 106

3,4-Dihydroxy-5-nitrobenzylthioacetic acid

A solution containing 1.0 g of 3,4-dihydroxy-5-nitrobenzylalcohol in 5.0 g of thioglycolic acid was stirred for 1.5 h at 120° C. 25 ml of water was added and product was filtered and washed with water. Yield 0.25 g (19%), m.p. 91°-93° C.

EXAMPLE 107

2-(3,4-Dihydroxy-5-nitrobenzyl)pyrrole

A solution containing 1.0 g of 3,4-dihydroxy-5-nitrobenzyl alcohol and 5.0 ml of pyrrole in 3.0 ml of dioxane was heated for 5 h at 100° C. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated and the residue was purified in a silicagel column using toluene-acetic acid-dioxane (18:1:1) mixture as an eluent. Yield 0.42 g (33%), m.p. 115°-118° C.

EXAMPLE 108

2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)propanol

To a solution containing 0.85 g of ethyl 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate (Example 81) in 70 ml of dry ethanol 0.3 g of sodium borohydride was gradually added. The solution was stirred for 0.5 h at room temperature, acidified with hydrochloric acid and extracted with ethyl acetate. The solvent was evapo-

rated yielding 0.55 g (75%) of yellow crystals, m.p. 149°-152° C.

EXAMPLE 109

3-Nitrocatechol

To a solution containing 2.5 g of catechol in 125 ml of ether 1.0 ml of conc. nitric acid (d-1.52) was gradually added. The solution was stirred over night at room temperature and washed with water. The solvent was evaporated and the residue was treated with boiling petroleum ether (b.p. 60°-80° C). The insoluble 4-nitrocatechol was filtered and the filtrate concentrated in vacuo. After cooling the 3-nitrocatechol was filtered. Yield 0.85 g (24%), m.p. 82°-85° C.

EXAMPLE 110

3,5-Dinitrocatechol

To a solution containing 50.0 g of catechol diacetate in 250 ml of acetic acid 125 ml of nitric acid (d-1.42) was gradually added at 50° C. The solution was stirred for 1.5 h more at 50° C. and poured then to crushed ice. The product was filtered, washed with water and dissolved in 500 ml of methanol containing 1.0 ml of conc. sulfuric acid. The solution was refluxed for 2.5 h. Methanol was distilled off to a great extend and 100 ml of water was added. The remaining methanol was evaporated in vacuo whereupon the product was crystallized. Yield 20.9 g (40.4%), m.p. 168°-170° C.

EXAMPLE 111

3,4-Dihydroxy-5-nitrobenzaldehyde

A solution containing 8.0 kg of 5-nitrovanillin and 8.7 kg of acetic acid in 35 kg of conc. hydrobromic acid was refluxed for 20 h. 0.6 kg of charcoal was added and the mixture was filtered. 32 kg of water was added with stirring and the solution was cooled to -10° C. and stirring was continued for 2 h more. The crystalline product was filtered and washed with water. Yield 5.66 kg (80%), m.p. 135°-137° C.

EXAMPLE 112

3,4-Dihydroxy-5-nitrobenzonitrile

A solution containing 0.92 g of 3,4-dihydroxy-5-nitrobenzaldehyde and 0.49 g of hydroxylamine hydrochloride in 5.0 ml of formic acid was refluxed for 1 h. 50 ml of water was added and the product was filtered and washed with water. Yield 0.3 g (33%), m.p. 175°-178° C.

EXAMPLE 113

4-Chloro-6-nitrocatechol

A mixture containing 1.0 g of 4-chloro-3-methoxy-6-nitrophenol in 20 ml of conc. hydrobromic acid was refluxed for 2 h. After cooling the product was filtered and washed with water. Yield 0.6 g (65%), m.p. 108°-111° C.

EXAMPLE 114

4,5-Dihydroxyisophthalaldehyde

To a suspension containing 1.8 g of 4-hydroxy-5-methoxyisophthalaldehyde in 20 ml of dichloromethane was added 35 ml of 1 molar PBr₃ in dichloromethane. The mixture was allowed to stand over night at room temperature and poured into ice-water. Dichloromethane was evaporated in vacuo. After cooling the product

was filtered and washed with wash. Yield 0.94 g (57%), m.p. 192°-195° C.

EXAMPLE 115

3,4-Dihydroxy-5-cyanobenzoic acid

To a solution containing 2.3 g of 4-acetoxy-3-cyano-5-methoxybenzoic acid in 10 ml of dichloromethane 40 ml of 1 molar PBr₃ in dichloromethane was added. The mixture was stirred over night at room temperature. The solvent was evaporated in vacuo and to the residue ice-water was added. The product was filtered and washed with water. Yield 1.25 g (74%), m.p. 269°-271° C.

EXAMPLE 116

3,4-Dihydroxy-5-nitrophenylalanine hydrobromide

A solution containing 1.2 g of 4-hydroxy-3-methoxy-5-nitrophenylalanine hydrosulfate in 10 ml of conc. hydrobromic acid was refluxed for 2 h. The solution was concentrated in vacuo and allowed to stand over night in a refrigerator. The product was filtered and washed with hydrobromic acid and dried. Yield 0.25 g, m.p. 170° C. (decomp.).

EXAMPLE 117

3,5-Dicyanocatechol

A solution containing 0.83 g of 3,5-diformylcatechol and 0.90 g of hydroxylamine hydrochloride in 30 ml of formic acid was refluxed for 16 hours. Formic acid was evaporated in vacuo and water was added to the residue. The solution was extracted with ether. The solvent was evaporated and the residue was crystallized from ethanol-water. Yield 0.28 g (43%), m.p. 300° C. (decomp.).

EXAMPLE 118

N,N-diethyl-5-chloro-2,3-dihydroxybenzenesulfonamide

To a solution containing 0.7 g of N,N-diethyl-5-chloro-3,4-dimethoxybenzenesulfonamide in 10 ml of dichloromethane 9.0 ml of 1 molar BBr₃ in dichloromethane was added. The solution was stirred overnight at room temperature. Water and hydrochloric acid were added and the mixture was extracted with dichloromethane. The solvent was evaporated. Yield 0.3 g (47%), m.p. 62°-64° C.

EXAMPLE 119

4-Chloro-6-methylsulfonylcatechol

The procedure described in Example 118 was repeated using 4-chloro-2-methoxy-6-methylsulfonylphenol. Yield 50%, m.p. 142°-145° C.

EXAMPLE 120

4-Nitro-6-methylsulfonylcatechol

The procedure described in Example 118 was repeated using 2-methoxy-4-nitro-6-methylsulfonylphenol. Yield 21%, m.p. 221°-224° C.

EXAMPLE 121

3,4-Dihydroxy-5-methylsulfonylbenzaldehyde

The procedure described in Example 118 was repeated using 4-hydroxy-3-methoxy-5-methylsulfonylbenzaldehyde. Yield 17%, m.p. 169°-171° C.

EXAMPLE 122

N-(3-hydroxypropyl)-3,4-dihydroxy-5-nitrobenzamide

The procedures described in Examples 43 and 44 were repeated using 3,4-diacetoxy-5-nitrobenzoic acid and 3-aminopropan-1-ol. Yield 85%, m.p. 160°-163° C.

EXAMPLE 123

Neopentyl

2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylate

The procedure described in Example 4 was repeated using 3,4-dihydroxy-5-nitrobenzaldehyde and neopentyl cyanoacetate. Yield 67%, m.p. 173°-179° C.

EXAMPLE 124

N-(3-hydroxypropyl)-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide

The procedure described in Example 99 was repeated using N-(3-hydroxypropyl)cyanoacetamide and 3,4-dihydroxy-5-nitrobenzaldehyde. Yield 52%, m.p. 223°-228° C.

EXAMPLE 125

2,3-Dihydroxy-5-nitrobenzonitrile

The procedure described in Example 118 was repeated using 2-hydroxy-3-methoxy-5-nitrobenzonitrile. Yield 45%.

EXAMPLE 126

3,5-Dicyanocatechol

To a solution containing 2,4-dicyano-6-methoxyphenol in 20 ml of dichloromethane 20 ml of 1 molar solution of BBr₃ in dichloromethane was added. The solution was stirred overnight at room temperature. Water and hydrochloric acid were added and the mixture was extracted with dichloromethane. The solvent was evaporated. Yield 0.8 g (50%), m.p. 300° C. (decomp.).

EXAMPLE 127

1,2-Diacetoxy-3,5-dinitrobenzene

A catalytic amount of concentrated sulfuric acid was added to a solution containing 2.0 g of 3,5-dinitrocatechol in 15 ml of acetic anhydride and the solution was mixed for ½ hours in 50°-60° C. Ice water was added to the reaction mixture and the solution was mixed in 0° C. whereby the product was crystallized. The product was filtered and washed with water and dried. Yield 2.75 g (97%), m.p. 115°-117° C.

EXAMPLE 128

1,2-Dipropionyloxy-3,5-dinitrobenzene

The procedure of Example 127 was repeated using propionic acid anhydride instead of acetic anhydride. Yield 2.8 g (90%), m.p. 72°-73° C.

EXAMPLE 129

1,2-Dibutyryloxy-3,5-dinitrobenzene

The procedure described in Example 127 was repeated using butyryl anhydride instead of acetic anhydride. Yield 70%, m.p. 65°-60° C.

EXAMPLE 130

2-Butanoyloxy-4,6-dinitrophenol

8.7 ml of nitric acid (d-1.42) was added stirring and cooling to a solution containing 2.4 g of catechol dibutyrate in 25 ml of acetic acid. The solution was stirred for further $\frac{1}{2}$ hours and ice water was added thereto. The product was filtered and washed with water. Yield 1.85 g (53%), m.p. 65°-70° C.

EXAMPLE 131

2-Pivaloyloxy-4,6-dinitrophenol

6.7 ml of nitric acid (d-1.42) was added stirring and cooling (in 20°-25° C.) to a solution containing 1.94 g of catechol monopivaloate in 20 ml of acetic acid. The solution was stirred for $\frac{1}{2}$ hours in 50° C. Ice water was added and the product was filtered and washed with water. Yield 1.75 g (62.5%), m.p. 132°-135° C.

EXAMPLE 132

2-Benzoyloxy-4,6-dinitrophenol

A mixture containing 2.0 g of 3,5-dinitrocatechol in 5 ml of benzoylchloride was cooked for 4 hours in 100° C. When cooled petroleum ether (b.p. 40° C.) was added and the product was filtered and washed with petroleum ether. The raw product was crystallized from ethanol. Yield 2.5 g (82%), m.p. 150°-152° C.

EXAMPLE 133

3-(4-Hydroxy-5-nitro-3-pivaloyloxybenzylidene)-2,4-pentanedione

A mixture containing 2.0 g of the product obtained according to Example 7 in 5 ml of pivaloylchloride was heated for 4 hours in 100° C. The excess pivaloylchloride was evaporated away in reduced pressure and ether was added to the residue. The product was filtered and washed with ether. Yield 1.41 g (58%), m.p. 143°-145° C.

EXAMPLE 134

2-(2,6-Dimethylbenzoyloxy)-4,6-dinitrophenol

A mixture containing 2.0 g of 3,5-dinitrocatechol in 5 ml of 2,6-dimethylbenzoylchloride was heated for 20 hours in 100° C. The excess 2,6-dimethylbenzoylchloride was removed in high vacuum. The residue was purified in silicagel column. Yield 1.5 g (45%), yellow viscous oil, which was crystallized from petroleum ether, m.p. 163°-165° C.

EXAMPLE 135

2-(2,6-Dimethoxybenzoyloxy)-4,6-dinitrophenol

The procedure of Example 134 was repeated using 2,6-dimethoxybenzoylchloride. Yield 1.3 g (36%), m.p. 217°-218° C.

EXAMPLE 136

2-(1-Methylcyclohexylcarbonyloxy)-4,6-dinitrophenol

The procedure of Example 134 was repeated using 1-methylcyclohexanecarboxylic acid chloride. Yield 1.6 g (49%), yellow

EXAMPLE 137

1,2-Bis(2,6-dimethylbenzoyloxy)-3,5-dinitrobenzene

The procedure of Example 134 was repeated using a temperature of 134° C. The product was crystallized from 50% ethanol. M.p. 175°-178° C. Yield 60%.

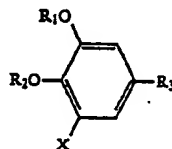
EXAMPLE 138

1,2-Bis(3-ethoxycarbonylpropionyloxy)-3,5-dinitrobenzene

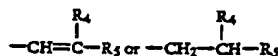
A solution containing 1 g of 3,5-dinitrocatechol in 2.5 ml of ethyl ester chloride of succinic acid was heated for 3 h in 100° C. The product was purified in silicagel column. M.p. 60°-63° C.

What is claimed is:

1. A compound according to formula I



wherein R₁ and R₂ independently represent hydrogen, carbamoyl which is substituted by an alkyl of 1 to 4 carbon atoms, alkylcarbonyl of 2 to 5 carbon atoms or phenyl carbonyl, X represents nitro or cyano and R₃ represents



wherein R₄ represents cyano or alkylcarbonyl of 2 to 5 carbon atoms and R₃ represents carbamoyl which is unsubstituted or substituted with alkyl of 1 to 8 carbon atoms or which is substituted with hydroxyalkyl of 1 to 8 carbon atoms or pharmaceutically acceptable esters and salts thereof.

2. The compound according to claim 1, wherein R₄ is cyano and R₃ is carbamoyl which is unsubstituted or substituted with alkyl of 1 to 3 carbon atoms.

3. N,N-diethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

4. A compound selected from the group consisting of 2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide, N,N-dimethyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide and N-isopropyl-2-cyano-3-(3,4-dihydroxy-5-nitrophenyl)acrylamide.

EXHIBIT 4



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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. **TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).**

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. **THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.**

| ITEM NBR | PATENT NUMBER | FEE CDE | FEE AMT | SUR CHARGE | SERIAL NUMBER | PATENT DATE | FILE DATE | PAY SML YR ENT | STAT |
|-------------|------------------|------------|------------|---------------|------------------|----------------|--------------|-------------------|------|
| 1 | 5,446,194 | 183 | 940 | ---- | 08/121,617 | 08/29/95 | 09/16/93 | 04 NO | PAID |

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**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
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EXHIBIT 5

**COMBINED DECLARATION AND POWER OF ATTORNEY
FOR UTILITY PATENT APPLICATION**

Attorney Docket No.

020325-030

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I BELIEVE I AM THE ORIGINAL, FIRST AND SOLE INVENTOR (if only one name is listed below) OR AN ORIGINAL, FIRST AND JOINT INVENTOR (if more than one name is listed below) OF THE SUBJECT MATTER WHICH IS CLAIMED AND FOR WHICH A PATENT IS SOUGHT ON THE INVENTION

ENTITLED: PHARMACOLOGICALLY ACTIVE COMPOUNDS, METHODS FOR THE PREPARATION
THEREOF AND COMPOSITIONS CONTAINING THE SAME

the specification of which

(check one)

☐ is attached hereto;

☒ was filed on November 27, 1987 as

Application Serial No. 07/126,911

11/27/87, 6/13/89,

and was amended on 11/28/89, 3/30/90 ;
(if applicable)

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE;

I ACKNOWLEDGE THE DUTY TO DISCLOSE INFORMATION WHICH IS MATERIAL TO THE EXAMINATION OF THIS APPLICATION IN ACCORDANCE WITH TITLE 37, CODE OF FEDERAL REGULATIONS, Sec. 1.56 (a) which states: "A duty of candor and good faith toward the Patent and Trademark Office rests on the inventor, on each attorney or agent who prepares or prosecutes the application and on every other individual who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application. All such individuals have a duty to disclose to the Office information they are aware of which is material to the examination of the application. Such information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. The duty is commensurate with the degree of involvement in the preparation or prosecution of the application.";

I do not know and do not believe the said invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application; that said invention was not in public use or on sale in the United States of America more than one year prior to said application; that said invention has not been patented or made the subject of an inventor's certificate issued before the date of said application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than twelve months prior to said application;

I hereby claim foreign priority benefits under Title 35, United States Code Sec. 119 and/or Sec. 365 of any foreign application(s) for patent or inventor's certificate as indicated below and have also identified below any foreign application for patent or inventor's certificate on this invention having a filing date before that of the application(s) on which priority is claimed:

| COMBINED DECLARATION AND POWER OF ATTORNEY | | Attorney Docket No. 020325-030 | |
|--|--------------------|--------------------------------------|---|
| COUNTRY/INTERNATIONAL | APPLICATION NUMBER | DATE OF FILING (day, month, year) | PRIORITY CLAIMED |
| FI | 864875 | 28 Nov 1986 | YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> |
| GB | 8712437 | 27 May 1987 | YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> |

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

| | | | | | |
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| | | | |
|---|--|---|-------------------|
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☒ Please see attached continuation page for additional inventors.

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